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**Title:** Phase II Study of the Anti-Mesothelin Immunotoxin LMB-100 Followed by Pembrolizumab in Malignant Mesothelioma

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**Investigational Agents:**

| | | |
|---|---|---|
| Drug Name: | LMB-100 | Pembrolizumab (Keytruda®) |
| IND Number: | 152907 | 152907 |
| Sponsor: | Center for Cancer Research | Center for Cancer Research |
| Manufacturer: | Selecta Biosciences | Merck |

**Commercial Agents**: None

## PRÉCIS

**Background:**

- LMB-100, and a closely related immunotoxin, SS1P, also targeting mesothelin, have been studied in previous Phase 1 clinical studies for mesothelioma and pancreatic cancer.
- LMB-100 has demonstrated anti-tumor efficacy against several mesothelin expressing tumor models including mesothelioma PDX models
- PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands
- 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.
- In immune-competent mice bearing human mesothelin expressing tumors local administration of LMB-100 with CTLA-4 blockade eradicates murine tumors by promoting anti-cancer immunity.
- LMB-100 treatment increase CD8+ T cell infiltration in murine lung adenocarcinoma tumors that express human mesothelin.
- Combination treatment with LMB-100 plus anti-PD1 results in greater anti-tumor efficacy in murine lung cancer model
- Pembrolizumab is an anti PD-1 antibody that has demonstrated responses of long duration in clinical trials and has generally been well-tolerated
- It is hypothesized that the anti-mesothelin immunotoxin LMB-100 followed by pembrolizumab will result in greater anti-tumor efficacy in patients with mesothelioma.

**Objectives:**

- To determine the objective response rate of sequential therapy with LMB-100 followed by pembrolizumab in subjects with pleural and peritoneal mesothelioma.

**Eligibility:**

- Histologically confirmed epithelial or biphasic pleural or peritoneal mesothelioma (with <50% sarcomatoid component) not amenable to potentially curative surgical resection.
- Subjects must have at least one prior chemotherapy regimen that includes pemetrexed and cisplatin or carboplatin.
- Age ≥ 18 years.
- ECOG performance status of 0 or 1.
- Adequate organ and bone marrow function
- Prior PD1/PD-L1 inhibitor treatment is prohibited
- Chemotherapy within 4 weeks or radiotherapy within 2 weeks prior to start of study therapy is prohibited.

- Subjects with active CNS metastasis are excluded
- Subjects with active autoimmune disease for which they had received systemic treatment during the previous 2 years receiving systemic glucocorticoids (excluding daily glucocorticoid-replacement therapy for conditions such as adrenal or pituitary insufficiency) are excluded
- Subjects with active interstitial lung disease, or a history of pneumonitis for which they had received glucocorticoids are excluded

**Design:**

- This is an open-label, single center phase II study of LMB-100 followed by pembrolizumab in subjects with advanced pleural or peritoneal mesothelioma who have progressed on standard therapies.
- Subjects will receive LMB-100 at the single agent MTD on days 1, 3 and 5 of a 21-day cycle for 2 cycles and pembrolizumab 200 mg on day1 of each subsequent 21-day cycle until disease progression (on or after pembrolizumab) or intolerable toxicity for a maximum of 2 years (unless second course initiated).
- Tumor biopsies will be performed at baseline, at the end of cycle 2 and at the end of cycle 4 to evaluate changes in the tumor immune microenvironment following treatment with LMB-100 and pembrolizumab.
- Up to 35 evaluable subjects will be enrolled

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 INTRODUCTION

## 1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the objective response rate of sequential therapy with LMB-100 followed by pembrolizumab in subjects with pleural and peritoneal mesothelioma.

1.1.2 Secondary Objectives

- Safety of sequential administration of pembrolizumab following LMB-100
- To determine the duration of response, progression free survival and overall survival.

1.1.3 Exploratory Objectives

- To establish the correlation of response with tumor mesothelin expression.
- To evaluate correlation of tumor response with tumor PD-L1 expression.
- To evaluate changes in the tumor microenvironment following treatment with LMB-100 and pembrolizumab.
- To evaluate the utility of serum mesothelin and megakaryocyte potentiating factor as a biomarkers of tumor response.
- To define the pharmacokinetics characteristics of LMB-100 in order to correlate responses with LMB-100 blood levels
- To determine the incidence of antibody development at the end of cycles 1 and 2 with this combination
- To evaluate MSI status in participants demonstrating objective response
- To determine the mechanism of capillary leak syndrome (CLS)

## 1.2 BACKGROUND AND RATIONALE

### 1.2.1 Hypotheses

- Anti-mesothelin immunotoxin LMB-100 followed by pembrolizumab will result in greater anti-tumor efficacy in subjects with mesothelioma by augmenting anti-tumor immunity.
- LMB-100 will induce tumor inflammation that leads to recruitment of CD8+ cells in the tumor and administration of pembrolizumab will increase the efficacy of these cytotoxic T cells.

### 1.2.2 Background on Mesothelioma

Mesothelioma is a neoplasm originating from the mesothelial cells lining human body cavities. Mesothelioma may involve the pleura and less frequently, the peritoneum. Approximately 3000 new cases are diagnosed every year in the US alone. The epithelioid variant is the most common, comprising about 60 percent of all mesotheliomas. Malignant pleural mesothelioma is an aggressive disease with poor prognosis. Although patients with a limited tumor burden may benefit from surgical resection, most patients have advanced disease at diagnosis and are not candidates for cytoreductive surgery.[1] For patients who are not eligible for curative surgery, the median survival with supportive care alone is 6 months whereas with the current standard treatment, a combination of cisplatin and pemetrexed, the median survival is 12 months.[2]

Peritoneal mesothelioma represents about one-fifth to one-third of all forms of mesothelioma; there are approximately 400 new cases in the United States each year.[3] Cytoreductive surgery and hyperthermic perioperative chemotherapy is the accepted initial management for suitable patients with peritoneal mesothelioma.[4-7] Peritoneal mesothelioma patients with surgically unresectable disease or whose medical co-morbidities preclude surgery are considered for palliative systemic therapy. Due to its relatively low incidence and inherent difficulties of radiologic assessment, few studies of systemic therapy have been conducted. Treatment recommendations are often extrapolated from pleural mesothelioma and outcomes are poor.

### 1.2.3 Mesothelin as a target for cancer therapy

Mesothelin is a glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein, which is present in a restricted set of normal adult tissues, such as the mesothelial lining of the pleura, peritoneum and pericardium.[8] Immunohistochemistry has shown that mesothelin is highly expressed in nearly all epithelioid mesotheliomas as well as epithelial components of biphasic mesothelioma in addition to pancreatic ductal adenocarcinomas and in a high percentage of epithelial ovarian cancers and non-small cell lung cancer (NSCLC).[9] Although the normal biological function of mesothelin is unknown, growing evidence suggests that it may play a role in tumorigenesis and metastasis. Its limited expression in normal human tissue and high expression in tumor makes mesothelin an excellent target antigen for antibody-based immunotherapy.[10]

Because of the high expression of mesothelin in many malignancies, a variety of agents are being developed to target mesothelin. Results of several ongoing clinical trials of immunotherapy agents directed against mesothelin have shown that targeting mesothelin is safe and does not result in toxicity to essential normal tissues. Both antibody-based therapies, as well as mesothelin vaccines, are being investigated.[11] The Laboratory of Molecular Biology (LMB) and the

Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute have pioneered the use of mesothelin- targeted agents and clinical trials over the last decade.

### 1.2.4 LMB-100:

Recombinant immunotoxins are therapeutic agents composed of an antibody fragment attached to a protein toxin derived from bacteria or plants. After entering the cell by endocytosis, the immunotoxin reaches the cytosol, where it inactivates elongation factor 2, arrests protein synthesis and induces apoptotic cell death. LMB-100 is a recombinant immunotoxin consisting of a humanized anti-mesothelin Fab fused to a 24kDa truncated *Pseudomonas* exotoxin A (PE) fragment with mutations that suppress B and T cell epitopes.[12] It has anti-tumor efficacy against several mesothelin expressing tumor models including mesothelioma PDX models.[13] Phase I clinical trial of LMB-100 has been completed at NCI and we have established the MTD, which will be used in combination studies with pembrolizumab.

#### 1.2.4.1 Rationale for the development of LMB-100

The clinical use of SS1P, and of immunotoxins in general, has been hampered mainly by their high immunogenicity which limits the number of effective treatment cycles that patients can receive. LMB-100 (see Figure 1 for structure) is a next generation PE-fusion protein that has been protein-engineered to maximally reduce its immunogenicity by:

1. Using a fully humanized Fab fragment derived from the anti-mesothelin antibody SS1 for tumor targeting
2. Substituting the bulk of domain II (residues 251–273 and 284–394 of native PE) by an extended furin cleavable linker whose sequence is devoid of any T cell neo-epitopes
3. Deimmunizing domain III of PE, which has the catalytic activity for ADP-ribosylation by introducing 7 point mutations that silence B- and T-cell epitopes

Classical PE-based immunotoxins, such as SS1P, contain a 38 kD fragment of the exotoxin encompassing the so-called translocation domain II and the catalytic domain III. Omission of the domain II from LMB-100 has not only removed a highly immunogenic 14 kD portion of PE that contains the main T-cell epitopes,[14] but has also resulted in reduced incidents of CLS in animal models of CLS.[15]

#### 1.2.4.2 Development of LMB-100:

LMB-100 (previously RO6927005 and RG7787) is a next generation anti-mesothelin RIT developed in NCI's Laboratory of Molecular Biology in collaboration with Roche (Figure 1). LMB-100 contains a newly engineered PE fragment that has improved activity against most mesothelin-expressing cancer cell lines in vitro, and is also much less toxic than SS1P in pre-clinical models. This improved therapeutic window allows administration of three to eight times the dose of RIT to mice, rats and monkeys compared to SS1P. The new PE contains modifications specifically designed to reduce immunogenicity of the molecule. This includes deletion of a 14 kD sequence that precedes the catalytic domain and seven point mutations within the catalytic domain itself. These changes ablate the major human B cell epitopes within the molecule and also the most antigenic T cell epitope.[15, 16] The anti-mesothelin targeting region of LMB-100 uses a humanized Fab fragment instead of the smaller dsFv fragment used in SS1P. This increases molecular weight of the RIT above the threshold required to prevent filtration by the kidney and increases half-life.

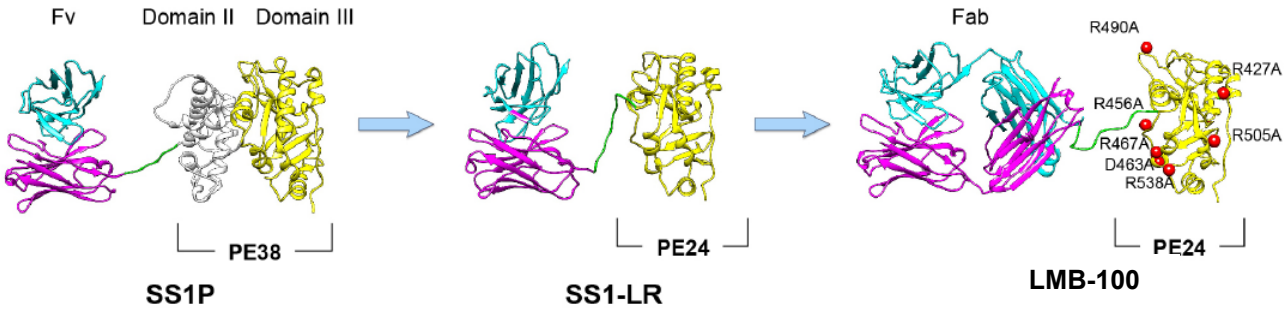



**Figure 1**. Structural models of SS1P and its de-immunized variants SS1P-LR and LMB-100 are shown.

The targeting domain consists of VL (cyan) and VH (magenta). The linker between the targeting domain and PE contains the furin cleavage site (green), which is required for toxin cytotoxic activity. The furin cleavage site is part of PE Domain II. The remainder of Domain II (gray) is unnecessary for cytotoxicity and has been deleted in the PE24-based toxins, SS1-LR and LMB-100. Domain III (yellow) is the catalytic domain of PE. In LMB-100, alanine point mutations were introduced at seven bulky hydrophilic residues (red) to silence human B cell epitopes within this domain. Deletion of Domain II reduces the size of the molecule into the range where it can be easily filtered by the kidneys, reducing serum half-life. LMB-100 contains a larger humanized Fab for targeting which raises its molecular weight above this threshold.

### 1.2.4.3 Nonclinical Studies

#### **1.2.4.3.1** Nonclinical Pharmacology

In vitro LMB-100 inhibited viability of a variety of mesothelin-positive cancer cell lines at effective concentrations typically around 14 pM (~1 ng/mL). The cytotoxic potency of LMB-100 varied between 0.35 ng/mL in primary mesothelioma cells (RH21) and 15.7 ng/mL in an adenosquamous lung carcinoma cell line (H596). Binding studies showed that while the Fab fragment did not bind to mouse or rat mesothelin, the binding affinities to cynomolgus and human mesothelin were identical. In agreement with this, LMB-100 induced apoptosis in mesothelin-positive primary cynomolgus pericardial cells and significantly impaired viability of HEK293 cells transfected with human mesothelin, but not of rat mesothelin transfected or untransfected HEK293 cells. In addition, control experiments showed that free PE24 was 100–1000 fold less potent on mesothelin-positive target cell lines, confirming low cytotoxic potential of PE24 lacking a targeting moiety.

LMB-100 showed broad activity against different mesothelin-expressing cancer cell lines and patient derived xenograft models.[12, 17]

Animal studies demonstrated that a single cycle of LMB-100 treatment given at an optimal dose of approximately 2 mg/kg, 3 × per week, every other day (QOD) achieved tumor regressions in subcutaneous xenografts of adenosquamous lung carcinoma (H596) in severe combined immunodeficient (SCID) beige mice. Three consecutive treatment cycles, given with 1 week breaks in between, led to massive shrinkage of large tumors with an average initial volume of 600 $mm^3$. Tumor regressions in monotherapy were also achieved when treating subcutaneous xenografts of mesothelioma (NCI-H226), gastric (MKN-28), and triple negative breast (HCC70) cancer cell lines in athymic nude mice. Highly synergistic antitumor efficacy was observed in combination therapy with paclitaxel when treating subcutaneous xenografts of the recombinant

high mesothelin expressing A431/H9 cell line or the pancreatic cancer cell line KLM1. Synergy was also observed in the HCC70 and MKN-28 cell lines. These results support evidence that LMB-100 in monotherapy or in combination with standard chemotherapies may provide clinical benefit to patients with cancer.

**1.2.4.3.2** Pharmacokinetics in Animals

The pharmacokinetics (PK) of LMB-100 were tested in cynomolgus monkeys following a single IV administration at doses ranging from 0.03 mg/kg to 0.3 mg/kg. Two different enzyme-linked immunosorbent based formats were used for analyzing plasma levels of LMB-100; free and total drug assay (where the total drug assay was the sum of free LMB-100 and LMB-100 complexed with binding molecules). LMB-100 showed a relatively rapid plasma clearance and a volume of distribution at steady-state similar to the plasma volume. Within the dose range tested, non-linear PK was observed for free drug with an extended half-life at higher doses (mean terminal half-life approximately 0.6 hours at 0.3 mg/kg compared to 0.3 hours at 0.03 mg/kg) suggesting saturation of MSLN-mediated clearance pathways. Clearance of total drug was consistently lower than that for free drug implying the presence of soluble binding partners such as soluble mesothelin and ADAs. Induction of anti-drug antibodies (ADA) responses was frequently detectable in all dose groups tested. Overall, given the limited predictive value of immunogenicity reactions in animals to human, a risk for immunogenicity in humans cannot be excluded. Toxico-kinetics after repeated IV dosing in cynomolgus monkeys demonstrated an increase in total exposure in a dose proportional manner between 0.1 mg/kg and 3.0 mg/kg. No accumulation was observed over 5 consecutive days of treatment or over two dosing cycles with 3 × per week dosing. Almost all monkeys developed ADAs upon treatment, while induction of high ADA levels impaired the exposure of free drug. In some cases, the induction of ADAs may have induced a slight increase in exposure

The relationship between systemic drug exposure and anti-tumor activity of LMB-100 was investigated on human lung cancer NCI-H596 xenograft growth in female SCID beige mice. Free and total drug profiles were similar in mice. Modeling estimated a plasma concentration of 6800 ng/mL (± 36%) to trigger a half maximal rate of tumor regression. Concentrations of LMB-100 above this level resulted in potent tumor regression after dosing. Normalized for exposure, SS1P was found to be ~3-fold more potent than LMB-100 in terms of tumor growth inhibition.

**1.2.4.3.3** Toxicology and Safety Pharmacology

The toxicological profile of LMB-100 was assessed after repeated intravenous administration to cynomolgus monkeys, the only relevant species, for a maximum of 5 daily doses for one week or 2 cycles with QOD × 3 dosing, separated by a 9-day dosing free period. Four daily doses of 3 mg/kg exceeded the maximum tolerated dose with animals being found in moribund condition, indicated by clinical signs of hypoactivity, hunched posture, ataxia, and tremors. There were no histopathological changes to account specifically for the deteriorating physical condition of these animals.

Histopathological findings such as kidney tubular degeneration/regeneration and changes at serosal-lining tissues were observed at lower doses as well. In general, administration of LMB-100 resulted in both on- and off-target toxicities.

On-target effects were observed on serosal-lining tissues, consistent with high expression of mesothelin. Mesothelium hypertrophy accompanied by subpleural cellular hypertrophy and

serosal fibrin exudate was observed in the lung at doses ≥ 1 mg/kg. Mesothelium hypertrophy also occurred in heart (epicardium), spleen, and stomach. Off-target or non-specific toxicity included degeneration/regeneration of kidney tubular epithelium after repeated doses of ≥ 0.3 mg/kg. Local inflammatory findings at the injection sites were observed after administration of LMB-100 in several studies. Clinically, reddening of the skin, swelling, and skin being warm to touch or flaky injection sites were reported. In the 2-cycle GLP study (3 intermittent doses over a 5-day period, 9-days apart), impaired movement of animals from all dose groups was likely related to injection site findings and an overall inflammatory profile. One female at 1 mg/kg was sacrificed early on Day 4 after 2 doses due to severe clinical signs most likely attributed to inflammatory changes at injection sites resulting in moribundity of the animal. Clinically observed inflammatory changes correlated with histopathological changes such as hemorrhages and/or acute inflammation at the injection sites and clinical pathology changes consistent with an overall inflammatory profile (increases in monocytes, neutrophils, CRP, and haptoglobin). Microscopic changes reversed completely after the 4-week recovery period in the 2-cycle GLP study. The Highest Non Severely Toxic Dose in this study was 0.3 mg/kg, which resulted in a mean AUC for total drug of 16.0 µg·h/mL (study day 1, preliminary data). In a subsequent 1 cycle GLP study (QOD × 3 dosing), markedly reduced Injection site findings were observed after administration of a batch with reduced levels of product related modifications of LMB-100. In this study, the HNSTD was 1 mg/kg, resulting in an AUC for total drug of 27.4 and 23.6 µg·h/mL after the first and third dose (preliminary data).

The potential of LMB-100 to induce off-target vascular leak in lungs was assessed in female Wistar rats. Mild perivascular edema was reported microscopically but did not correlate with macroscopic or serum chemistry findings consistent with CLS. Ultrasound evaluation in the NHP GLP study revealed minimal accumulation of pericardial fluid with limited biological significance at the highest dose of 1 mg/kg. No appreciable accumulation of pleural fluid was observed at necropsy.

In vitro evaluation of LMB-100 in human whole blood assay indicated a low risk for cytokine-mediated infusion related reaction (IRR)/cytokine release syndrome (CRS) upon first administrations. LMB-100 caused no hemolysis when added to human peripheral blood up to the highest concentrations of 0.5 mg/L.

#### 1.2.4.4 Clinical testing of single agent LMB-100 (Roche Study)

Initial clinical testing of LMB-100 was performed by Roche in a multi-center international first in human trial (NCT02317419). The primary objective of the Phase I study was to define the safety and tolerability (including the MTD) and pharmacokinetics of the drug in participants with MSLN-expressing metastatic or locally advanced solid tumors for whom no standard therapy was available. Secondary objectives included determination of the RP2D and schedule, exploration of preliminary anti-tumor activity by assessing objective response rate (ORR) and disease control rate (DCR), and assessment of pharmacodynamic effects.

A total of 15 participants were enrolled onto the study before termination. Median age of participants was 60.8 years and 53.3% were female. All participants had received prior anti-cancer therapy for their tumors. Enrolled participants had advanced mesothelioma (7), ovarian cancer (3), pancreatic cancer (3), and gastroesophageal cancer (2). Tumors from 13 of the 15

participants treated had moderately to strongly positive MSLN expression as measured by central IHC analysis.

LMB-100 was administered intravenously on Days 1, 3 and 5 of a 21-day treatment cycle. No pre-medications were given. Treatment was initiated at the MTD of SS1P, 45 mcg/ kg. Five different dose levels were tested (see Table 1). Dose limiting toxicity (DLT) was reached at 250 mcg/kg, with 2 of 4 participants treated at this dose level experiencing capillary leak syndrome (grade 2 and grade 4). Additional toxicities were associated with this dose level. At this point, a sixth cohort receiving 200 mcg/kg of study drug was enrolled, however, the study was terminated by the company before the two accrued participants completed cycle 1 of therapy. Therefore, the single agent MTD was not determined.

**Table 1**. **LMB-100 Dose escalation study- NCT02317419**

| Dose (mcg/kg) | No. of patients | Pts with DLT |
|---|---|---|
| 45 | 1 | 0 |
| 65 | 1 | 0 |
| 100 | 3 | 0 |
| 170 | 4 | 0 |
| 200 | 2 | NE |
| 250 | 4 | 2 |

DLTs were capillary leak syndrome and proteinuria

NE, Study terminated before DLT assessment period was complete and patients only received single dose of LMB-100

1.2.4.4.1 LMB-100 Adverse Events

Overall, 14 participants (93.3%) experienced at least one AE. The most common AEs were hypoalbuminemia (60.0%), fatigue (53.3%), peripheral edema (53.3%), nausea (46.7%), pyrexia (40.0%), decreased appetite (33.3%), dyspnea (33.3%), and myalgia (33.3%). SAEs included capillary leak syndrome, pyrexia, atrial flutter/fibrillation, infusion related reaction, arthritis, glomerulonephritis minimal lesion and dyspnea. No participants experienced an AE that led to withdrawal of study treatment. Four participants experienced a total of 8 infusion-related reactions that were independent of drug dose level. These AEs were non-serious and resolved within approximately 1 hour of onset. Pre-medication for infusion reaction was administered to these participants prior to subsequent doses of LMB-100. Two suspected Type III hypersensitivity reactions were observed. These consisted of arthritis (1 patient) and rash with fever (1 patient), both of which were fully reversible. When other AEs attributed to the study drug are presented by dose level of drug, it becomes clear that toxicity was strongly associated with the 250 mcg/kg dose level at which DLT was reached. Two of four patients treated at 250 mcg/kg experienced serious CLS which manifested with hypotension, respiratory compromise, serosal membrane reaction and hyponatremia as well as the hypoalbuminemia and edema that can be seen with mild CLS. Other symptoms associated with the DLT dose were fatigue, nausea, vomiting, decreased appetite and mild elevation of transaminases.

1.2.4.5 Clinical testing of single agent LMB-100 at NCI (Study 16C0127 -ongoing)

As of September 24, 2018, twenty-one patients were enrolled on the study. Ten patients were treated with single agent LMB-100; 11 with a combination of LMB-100 plus nab-paclitaxel. Of these 21 patients 12 had peritoneal mesothelioma and 9 pleural mesothelioma; 12 female and 9 male. The first 3 patients were treated at dose level 1 i.e. 170 mcg/kg with patient #1 initiating treatment on July 28, 2016. All three patients at this dose level during cycle 1 had grade 1 or 2 increase in serum creatinine). Since increase in serum creatinine was a common toxicity pattern at this dose level it was defined as DLT per protocol established criteria. The protocol was subsequently amended to allow the treating these three patients at dose level -1 (140 mcg/kg) during cycle 2-4 though the protocol prior to the amendment would have allowed retreatment at 170 mcg/kg as long as they met inclusion criteria for the study especially adequate renal function, defined in the protocol as creatinine clearance (by Cockcroft Gault formula) $\geq$50 mL/min. However, we felt it would be safer to re-treat these patients at dose level-1 instead of dose level 1 and adjusted the dose modification section of the protocol accordingly.

All subsequent patients have been treated at 140 mcg/kg. Of the 21 patients; 9 patients were taken off treatment due to disease progression; 8 completed the study with stable disease. Out of the 21 patients who received treatment on this study, 9 are still alive. The single agent MTD of LMB-100 was established as 140 mcg/kg given on days 1, 3 and 5 of a 21-day cycle.

Grade 2 infusion reactions were seen in 6 patients at some point during the treatment with LMB-100. In 3 patients it was seen during cycle 2, and in the remaining patients t during cycle 3 or cycle 4 . In most case the infusion reaction was managed by administration of dexamethasone and increasing infusion duration as per protocol. However, in two patients who had infusion reaction during cycle 4 of LMB-100 the treatment was discontinued. In one patient under Arm B who received 2 cycles of LMB-100 and 6 cycles of nab-paclitaxel, LMB-100 was held for cycle 2 day 5 after a reaction in cycle 2 day 3.

The most frequently occurring events were hypoalbuminemia (22% of 278 events) anemia (14%) lymphocyte count decreased (13%), hypophosphatemia (5%)Most of the events were grade 2. There was one serious grade 3 thromboembolic event; however, it was not attributed to the IND.

1.2.4.5.1 Pharmacokinetics of LMB-100:

Free LMB-100 plasma concentrations were measured with a validated ELISA with a lower limit of quantification of 2.1 ng/mL. Doses ranged from 140 mcg/kg – 170 mcg/kg. Samples for pharmacokinetic (PK) analysis were obtained from patients at pre-dose, end of infusion (EOI; 30-min post start), and 1 hour, 2 hours, 3 hours, 4 hours and 6 hours post EOI. Concentration data for each dose was plotted over time to assess the impact of increasing anti-drug antibodies (ADAs) that are generated in response to LMB-100 exposure. PK analysis for the 10 patients treated with single agent LMB-100 is shown in Table 2 below. Measured LMB-100 plasma concentrations were consistent during the first week of treatment, with a near dose-proportional increase in $C_{MAX}$ from 140 mcg/kg to 170 mcg/kg. However, the suspected generation of ADAs greatly reduced LMB-100 exposure by cycle 2.

As shown in Table 2, all 10 patients had good LMB-100 blood levels during cycle 1. However, only 5 of 10 patients had good blood levels during cycle 2. None of the 8 patients who got cycle 3 and 4 of LMB-100 had good LMB-100 blood levels during cycle 3 or 4.

**Table 2. Decrease in LMB-100 Exposure Over Time**

| Patient | C1D1 | | C2D1 | | C3D1 | | C4D1 | |
|---|---|---|---|---|---|---|---|---|
| | Dose (µg/kg) | Cmax (ng/mL) | Dose (µg/kg) | Cmax (ng/mL) | Dose (µg/kg) | Cmax (ng/mL) | Dose (µg/kg) | Cmax (ng/mL) |
| 1 | 170 | 1991 | 140 | 1091 | 140 | 21 | 140 | 21 |
| 2 | 170 | 2286 | 140 | 297 | 140 | 70 | 140 | 21 |
| 3 | 170 | 2760 | 140 | 4.4 | 140 | BQL | 140 | BQL |
| 4 | 140 | 1054 | 140 | 681 | 140 | BQL | 140 | BQL |
| 5 | 140 | 1124 | 140 | BQL | 140 | – | 140 | – |
| 6 | 140 | 2584 | 140 | 1099 | 140 | BQL | 140 | BQL |
| 7 | 140 | 3118 | 140 | 2450 | 140 | BQL | 140 | BQL |
| 8 | 140 | 1721 | 140 | BQL | 140 | BQL | 140 | BQL |
| 9 | 140 | 1526 | 140 | 27.8 | 140 | 20 | 140 | BQL |
| 10 | 140 | 2689 | 140 | 5.1 | 140 | N/A | 140 | N/A |

***** BQL: below assay's quantifiable limit (2.1 ng/mL); **–** Because of disease progression patient did not receive cycle 3 and 4; N/A: data not available

Note: Anti-drug (LMB-100) antibodies (ADAs) were measured pre-dose on C1D1. Inhibition percentages ≥41.8% indicate presence of pre-existing ADAs

These results show that all patients can have good blood levels during cycle 1 and half had detectable blood levels during cycle 2. These results are in agreement with the Roche phase I clinical trial. It is also clear that administration of LMB-100 beyond cycle 2 is unlikely to result in meaningful clinical benefit since there are no detectable blood levels during cycle 3 and 4.

### 1.2.5 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of malignancies because of its mechanism of action to bind the PD-1 receptor on the T cell.

#### 1.2.5.1 Pharmaceutical and Therapeutic Information

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades.[18] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.[19, 20]

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[21, 22]

The structure of murine PD-1 has been resolved.[23] PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.[22, 24-26] The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.[27, 28] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mesothelioma.

#### 1.2.5.2 Preclinical and Clinical Trial Data

##### 1.2.5.2.1 Preclinical Studies

**Safety**

The nonclinical toxicity studies consisted of pivotal 1-month and a 6-month repeat-dose chronic toxicity studies with 4-month recovery periods in Cynomolgus monkeys. These studies were supported by toxicokinetic evaluation of pembrolizumab. Additional evaluation included 2 in vitro tissue cross-reactivity studies with pembrolizumab in normal human and Cynomolgus monkey tissues, respectively, and immunotoxicology testing using surrogate antimurine PD-1 mAb in a TDAR study in mice to address whether treatment with anti-PD-1 would result in potential immune-mediated toxicity following vaccination and recall responses. There were no findings of toxicological significance in any of the conducted studies.

**Pharmacology**

No traditional metabolism studies were conducted with pembrolizumab per current ICH S6 (R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. However, in vivo studies were conducted in C.B17 SCID mice to demonstrate the lack of Fab-arm or half molecule exchange for pembrolizumab. IgG4 wild-type molecules can undergo in vitro and in vivo molecular rearrangement called Fab-arm (or half molecule) exchange by swapping their half molecule with other IgG4 half molecules, thereby generating bispecific or hybrid antibodies.[29, 30] A point mutation (S228P) in the core hinge region in IgG4 has been shown to be sufficient to prevent the Fab-arm exchange.[29, 30] The results supported that pembrolizumab, which has a hinge mutation from S to P at position 228, did not form detectable hybrid antibodies with co-administered wild type IgG4 molecules in vivo in SCID mice (PK007). This observation is consistent with the results of extensive in vitro characterization of pembrolizumab (PK007) and indicates that pembrolizumab is not likely to engage in Fab-arm exchange in humans.

**Assessment of Effects of PD-1 Blockade as Monotherapy and in Combination with Chemotherapy in Mouse Syngeneic Tumor Models**

Antimouse PD-1 J43 was tested as a monotherapy in the MC38 (colon adenocarcinoma in C57Bl/6 mice), C1498 (acute myeloid leukemia in C57Bl/6 mice), PDV6 (squamous cell carcinoma in C57Bl/6 mice), and A20 (B cell lymphoma in BALB/c mice) syngeneic mouse tumor models. In all monotherapy experiments, tumor cells were implanted subcutaneously in syngeneic hosts and were staged at 50 to 80 mm3 before dosing was initiated. Antimouse PD-1 or isotype control antibody was administered intraperitoneally every 3 to 4 days for a total of 5 treatments. Efficacy was determined by monitoring tumor volumes and long-term survival for each experimental group. PD-1 blockade demonstrated antitumor efficacy in each of these syngeneic tumor models.

Anti-PD-1 therapy also enhanced the effect of chemotherapeutic agents such as gemcitabine and 5-FU with combination therapy resulting in increased efficacy and increased complete regression rates in vivo.

In this study, MC38 colon adenocarcinomas were staged to approximately 100 to 120 mm3 before initiation of concurrent treatment with 5-FU (40 mg/kg) and antimouse PD-1 (10 mg/kg), both administered intraperitoneally once every 3 days for a total of 5 injections.

The combined treatment of MC38 colon adenocarcinomas with 5-FU and antimouse PD-1 showed a significant increase in antitumor efficacy over the individual monotherapy groups.

This increased efficacy was reflected in a 60% complete regression rate in the combined treatment protocol. In the monotherapy groups, anti–PD-1 alone induced 20% (2 out of 10) complete responses, whereas none of the mice treated with control antibody or 5-FU plus control antibody demonstrated complete regression. PD-1 blockade using the antimouse PD-1 J43 surrogate antibody in combination with gemcitabine also showed enhanced efficacy in the mouse MC38 colon adenocarcinoma tumor model.

1.2.5.2.2 Clinical Investigations

**Pharmacokinetics**

Pembrolizumab PK samples have been obtained from multiple trials for various tumor types including melanoma, NSCLC, HNSCC, UC and microsatellite instability high (MSI-H) tumors. The doses tested in these tumor types include one or more of the following doses: 2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg every 2 weeks (Q2W), and 200 mg Q3W.

The PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low CL and a limited central volume of distribution (Vc).[31-33] The estimates of between subject variability are low-to-moderate and are within the range of historically reported variability levels for mAbs. A recent review of mAbs reported the between subject variability range of 15% to 65% for CL and a median (range) of 26% (12%– 84%) for Vc.[31]

Steady-state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.

As pembrolizumab is an IgG4 antibody that is administered parentally and cleared by catabolism, food and drug-drug interactions (DDI) are not anticipated to affect exposure. Therefore, no dedicated DDI studies have been performed. However, as systemic corticosteroids may be used to treat immune-mediated adverse reactions concomitant with pembrolizumab, the potential for a PK DDI with pembrolizumab as a victim was assessed. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure.

**Safety**

Pembrolizumab has been granted approval in a number of markets and indications and has an established safety profile.

The overall safety profile of pembrolizumab is derived primarily from a locked and verified dataset with pooled data from monotherapy clinical trials (n-2799) in melanoma and NSCLC, as part of the product development of pembrolizumab.

In addition, the manufacturer continues to analyze data from other ongoing and completed clinical trials, as well as from the post marketing environment.

The mechanism of action of pembrolizumab involves the interruption of the binding of PD-1 to its ligands, thereby interrupting the down-modulation of T-cell immune response. It is therefore anticipated that ARs associated with pembrolizumab would include immune-mediated AEs. Based upon the mechanism of action, Merck developed a broad list of immune-mediated adverse events of special interest (AEOSI) to evaluate and monitor. Additionally, though not immune-mediated, infusion-related reactions are also included in the AEOSI list. Based on ongoing monitoring, Merck has identified those AEOSIs that have been observed and assessed as related to pembrolizumab. These events form the basis of the current safety profile for the product.

In addition, several AEOSIs (encephalitis, myocarditis, myasthenic syndrome, sarcoidosis, as well as the further characterization of severe skin reactions to include fatal Stevens Johnson Syndrome [SJS] and toxic epidermal necrolysis [TEN]) have been identified from data sources primarily outside the verified dataset.

The majority of participants, 2727 or 97.4%, experienced 1 or more AEs, and 2062 (73.7%) experienced 1 or more AEs reported as drug-related by the investigator. The percentage of

participants who experienced SAEs was lower; 1042 (37.2%) of participants experienced 1 or more SAEs; 334 (11.9%) participants discontinued due to an AE, and 282 (10.1%) participants experienced a drug-related SAE, as determined by the investigator.

The 5 most frequently reported AEs were: fatigue (37.3%), nausea (24.5%), decreased appetite (22.5%), diarrhea (22.3%), and cough (22%). The 5 most frequently reported SAEs were pneumonia (3.0%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%) and pulmonary embolism (1.5%).

The 5 most frequently reported AEs considered drug related by the investigator were fatigue (24.2%), pruritus (16.7%), rash (13.8%), diarrhea (12.3%), and nausea (10.9%). The 5 most frequently reported SAEs considered drug-related by the investigator were pneumonitis (1.6%), colitis (0.9%), diarrhea (0.6%), pyrexia (0.4%), and autoimmune hepatitis (0.3%).

The core risk profile of pembrolizumab was updated in IB v. 15 based on post-marketing data through 31-MAR-2017 to add a new potential risk of graft versus host disease (GVHD) after pembrolizumab in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). A further update was made based on data through 03-SEP-2018 to add Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis as adverse drug reactions.

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%). Furthermore, the frequency of immune-mediated AEOSIs is low, and these events are readily managed in the clinical setting.

**Efficacy**

Pembrolizumab monotherapy and combination therapies have been administered to participants with hematologic malignancies and solid tumors in Merck-sponsored trials.

Approved indications include: melanoma, NSCLC, HNSCC, cHL, UC, gastric/gastroesophageal junction cancer MSI-H tumors. Efficacy was not shown in multiple myeloma in combination with lenalidomide or pomalidomide and low-dose dexamethasone. Pembrolizumab as monotherapy or in combinations is being studied in various indications.

For the treatment of unresectable or metastatic melanoma, pembrolizumab demonstrated superior efficacy over available treatment options (IPI, Investigator's choice chemotherapy) in participants with advanced melanoma who were treatment-naïve, as well as those who progressed on prior therapy, including ipilimumab.

Pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. In previously treated participants with PD-L1 TPS ≥1% and disease progression following platinum-containing chemotherapy, pembrolizumab provided a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy. For participants with previously untreated metastatic NSCLC whose tumors express high levels of PD-L1, pembrolizumab demonstrated significant improvements in PFS and OS over standard of care chemotherapy.

Pembrolizumab in combination with pemetrexed/carboplatin for the first-line treatment of metastatic nonsquamous NSCLC demonstrated both a statistically significant and clinically meaningful difference in ORR and a statistically significant benefit in PFS compared with pemetrexed/carboplatin alone.

For the treatment of advanced HNSCC in a heavily pretreated population, pembrolizumab demonstrated a clinically meaningful response rate and a prolonged duration of response that is substantially distinct from what is expected with standard of care in previously treated participants with HNSCC, and points to the meaningful clinical benefit of pembrolizumab.

Pembrolizumab for the treatment of relapsed or refractory cHL, has demonstrated durable, robust, clinically meaningful responses in this heavily pretreated population that generally included standard front-line therapies, salvage therapies, auto-SCT if eligible with chemosensitive disease, other single agent or combination chemotherapy regimens as needed, and with or without brentuximab vedotin (BV). For the treatment of UC in participants who have not received prior chemotherapy and are cisplatin-ineligible, pembrolizumab demonstrated a clinically meaningful ORR in participants with locally advanced or metastatic UC. In participants with locally advanced or metastatic UC who have received platinum-containing chemotherapy, treatment with pembrolizumab demonstrated a significant improvement in OS and a clinically meaningful benefit in durable responses compared with standard of care therapies.

In participants with MSI-H tumors, pembrolizumab provided evidence of clinically meaningful benefit over standard treatments, regardless of tumor histology.

Data from early phase trials indicate that pembrolizumab has efficacy in mesothelioma with disease control rates of 72-77% and objective response rates of 20-21%. Likewise, the responses have been found to be durable, with the median duration of response being 12 months.[34, 35]

### 1.2.6 Rationale for Combination Therapy

**Combining local immunotoxin targeting mesothelin with CTLA-4 blockade synergistically eradicates murine cancer by promoting anti-cancer immunity.**

The Pastan lab has constructed a murine breast cancer cell line expressing human mesothelin (66C14-M) which grows in BALB/c transgenic mice expressing human mesothelin. The immunotoxins SS1P (first generation anti-mesothelin immunotoxin) or RG7787 (also called LMB-100) were injected directly into established tumors and anti-CTLA-4 administered intra-peritoneally. No cures occurred with CTLA-4 or immunotoxin SS1P/RG7787 alone. Combining anti-CTLA-4 with PBS, transient tumor shrinkage was observed in 1 of 6 mice and no complete remissions were obtained. However, combining anti–CTLA-4 and LMB-100 resulted in tumor size reduction in 11 of 13 mice, and complete tumor elimination in 8 of 13 mice (61%). Combining anti-CTLA-4 with SS1P resulted in the similar enhanced anti-tumor effects compared to single drug administration. LMB-100-I, an inactive mutant form of LMB-100. was tested as control. Only 1 of 13 mice achieved a complete remission when treated with LMB-100-I and anti–CTLA-4, suggesting cell killing by the immunotoxin is required for the antitumor effect (Figure 2). Mechanistic studies showed that combination treatment induced tumor regression was associated with increased numbers of tumor infiltrating $CD8^+$ cells. Surviving

mice were protected from tumor re-challenge by 66C14 cells not expressing mesothelin, indicating the development of anti-tumor immunity.

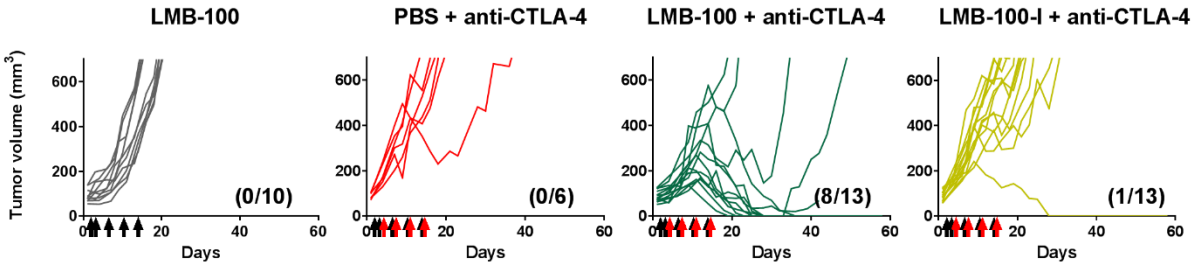
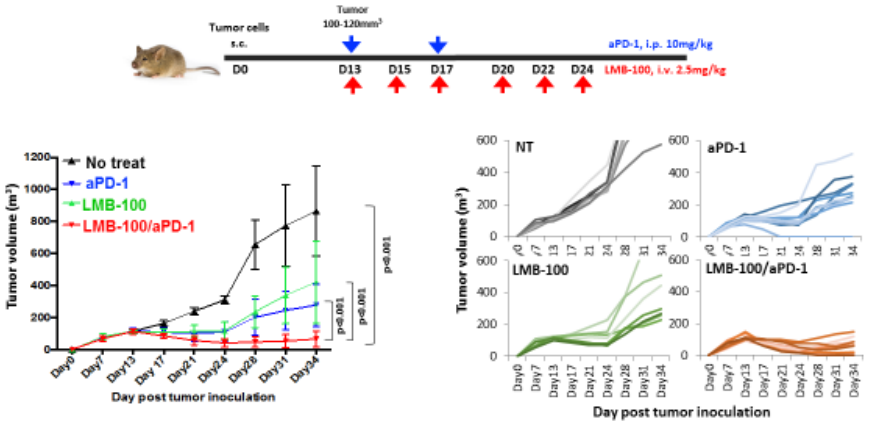



**Figure 2: LMB-100 and anti-CTLA-4 produces complete remissions but inactive LMB-100 (LMB-100-I) does not.**

**Systemic LMB-100 administration plus anti-PD1 blocking antibody shows increased anti-tumor efficacy.**

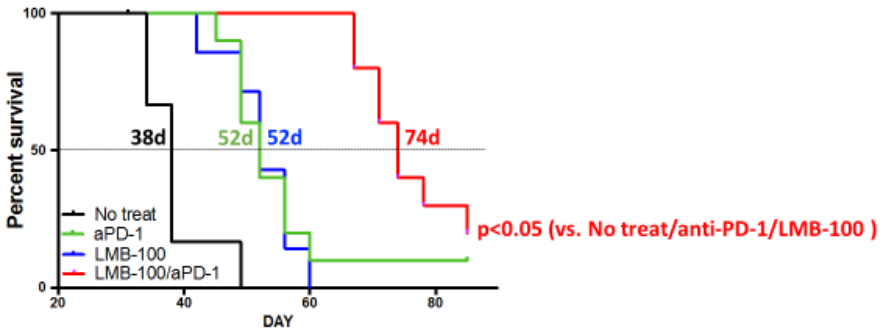
The Hassan lab has established a mouse syngeneic lung adenocarcinoma model expressing human mesothelin for studies of anti-mesothelin agents with immune-checkpoint inhibitors. Using this model, we observed increased anti-tumor efficacy of LMB-100 given systemically with anti-PD-1 antibody. As shown in Figure 3, LMB-100 was intravenously administered for 2 cycles (at a dose of 2.5mg/kg dose every other day for 3 times with cycle interval of 3 days). Anti-PD-1 antibody 10 mg/kg was administered i.p. twice with interval of 4 days between first and second dose. All the drug treatments were started when tumor size reached 100-120mm$^3$. Combination therapy with LMB-100 and anti-PD-1 antibody resulted in greater tumor regression compared to treatment with LMB-100 or anti-PD-1 alone. Furthermore, treatment with LMB-100 plus anti-PD-1 antibody significantly prolonged overall survival (74 days) compared to no drug treatment (38 days) or treatment with LMB-100 or anti-PD-1 antibody alone (52 days) (Figure 4). The precise mechanism of synergy is not understood at this time, but could be due to an abscopal effect from LMB-100.

**Figure 3: Combination therapy with LMB-100 plus anti-PD-1 antibody results in synergistic anti-tumor efficacy in hMSLN expressing mouse syngeneic lung cancer model**




Hassan R (confidential data; May 2, 2017)

**Figure 4: Treatment with LMB-100 plus anti-PD-1 antibody improves overall survival in hMSLN expressing mouse syngeneic lung cancer model**




* Survival time defined as the time for tumors to reach a volume of 1200 mm$^3$.

Hassan R (confidential data; May 2, 2017)

### 1.2.7 Justification for Study Doses

#### 1.2.7.1 LMB-100

The planned LMB-100 dose is the recommended single agent dose from the phase 1 study of LMB-100 (NCT02798536) established at 140 mcg/kg, on days 1, 3 and 5 of a 21-day cycle. Only two cycles of LMB100 will be administered as it is anticipated that a majority of patients will develop neutralizing antibodies after 2 cycles of treatment.

#### 1.2.7.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

**Summary**

In summary, our laboratory studies show remarkable synergy between LMB-100 and immune checkpoint inhibitors using local or systemic administration with anti-CTLA4 or anti-PD1 blocking antibodies. Based on clinical trials of pembrolizumab in subjects with treatment

refractory pleural mesothelioma that show a response rate of 20% we propose a clinical trial of this combination to determine if administration of LMB-100 can improve the response rates seen with pembrolizumab alone i.e. improve response rate from 20% to 40%. Since the anti-tumor efficacy of pembrolizumab in patients with peritoneal mesothelioma is not know we have separated these patients into a separate cohort to get preliminary estimates of anti-tumor activity of this combination in this patient population.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

### 2.1.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply.

2.1.1.1 Male and female participants who are at least 18 years of age on the day of signing the informed consent will be enrolled in the study.

2.1.1.2 Subjects must have histologically confirmed diagnosis of:

2.1.1.2.1 Cohort 1: Histologically confirmed epithelial or biphasic pleural mesothelioma (with <50% sarcomatoid component) not amenable to potentially curative surgical resection. The diagnosis will be confirmed by the Laboratory of Pathology, CCR, NCI.

OR

2.1.1.2.2 Cohort 2: Histologically confirmed epithelial or biphasic peritoneal mesothelioma (with <50% sarcomatoid component) not amenable to potentially curative surgical resection. The diagnosis will be confirmed by the Laboratory of Pathology, CCR, NCI.

2.1.1.3 Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.

2.1.1.4 Have measurable disease based on RECIST 1.1 (see Section 6.3). Lesions in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

2.1.1.5 Subjects must have at least one prior chemotherapy regimen that includes pemetrexed and cisplatin or carboplatin.

2.1.1.6 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See Appendix A. Evaluation of ECOG is to be performed within 7 days prior to start of study therapy.

2.1.1.7 Have adequate organ and marrow function as defined below:

| System | Laboratory Value |
|---|---|
| Hematological | |
| – hemoglobin | ≥ 9 g/dL or ≥5.6 mmol/L[a] |
| – absolute neutrophil count | ≥ 1,500/mcL |
| – platelets | ≥ 100,000/mcL |
| Hepatic | |
| – total bilirubin | ≤ 2.5 X institutional ULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 X ULN |
| – AST and ALT | ≤ 2.5 X institutional ULN (≤ 5 X ULN for participants with liver metastases) |
| Renal | |
| – Creatinine OR<br>– Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl) | ≤1.5 × ULN OR<br>≥ 50 mL/min for participant with creatinine levels > 1.5 X institutional ULN |
| Coagulation | |
| – International normalized ratio (INR) OR prothrombin time (PT)<br>– Activated partial thromboplastin time (aPTT) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants |

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

a. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

b. Creatinine clearance (CrCl) or eGFR should be calculated per institutional standard.

2.1.1.8 Must have left ventricular ejection fraction >50%.

2.1.1.9 Must recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

2.1.1.10 Must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

2.1.1.11 If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

2.1.1.12 The effects of LMB-100 on the developing human fetus are unknown. For this reason and because anti-PD-1 antibodies such as pembrolizumab are assumed to be teratogenic:

2.1.1.12.1 A male participant must agree to use contraception as detailed in see Appendix B of this protocol during the treatment period and for at least 180 days after the last dose of study treatment and refrain from donating sperm

2.1.1.12.2 A female participant is eligible to participate if she is not pregnant (see Appendix B), not breastfeeding, and at least one of the following conditions applies:

a. Not a woman of childbearing potential (WOCBP) as defined in Appendix B

OR

b. A WOCBP who agrees to follow the contraceptive guidance in Appendix B during the treatment period and for at least 180 days after the last dose of study treatment.

2.1.1.12.3 Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.13 The participant provides written informed consent for the trial.

2.1.2 Exclusion Criteria

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

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

2.1.2.2 Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

2.1.2.3 Has severe hypersensitivity (≥Grade 3) to pembrolizumab, LMB-100 and/or any of their excipients.

2.1.2.4 Subjects who have received prior therapy with LMB-100, an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).

2.1.2.5 Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to start of study therapy.

2.1.2.6 Has received prior radiotherapy within 2 weeks of start of study treatment.

2.1.2.7 Has had a prior pneumonectomy

2.1.2.8 Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles,

mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

2.1.2.9 Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to start of study therapy.

2.1.2.10 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g.., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

2.1.2.11 Has a history of (non-infectious) pneumonitis/interstitial lung disease(ILD) that required steroids or has current pneumonitis/ILD

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

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

2.1.2.14 A WOCBP who has a positive urine pregnancy test within 72 hours prior to start of study therapy (see Appendix B). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. **Note:** in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

2.1.2.15 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of trial treatment. Pregnant women are excluded from this study because LMB-100 + pembrolizumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with LMB-100 + pembrolizumab, breastfeeding should be discontinued if the mother is treated with LMB-100 + pembrolizumab. These potential risks may also apply to other agents used in this study.

2.1.2.16 Has a known history of Human Immunodeficiency Virus. HIV positive patients will be excluded due to a theoretical concern that the degree of immune suppression associated with the treatment may result in progression of HIV infection. (Note: No HIV testing is required)

2.1.2.17 Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. or active HBV or HCV infection. (Note: No testing for Hepatitis B and Hepatitis C is required.)

2.1.2.18 Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

2.1.2.19 Has an active infection requiring systemic therapy.

2.1.3 Recruitment Strategies

Information about the study will be posted on NIH sites such as clinicaltrials.gov and the CCR recruitment website. The study will also be publicized on various NIH social media platforms. Subjects will also be drawn from patients seen at the mesothelioma clinic at the NIH Clinical Center as well as from referrals from outside providers.

## 2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **12.6.1**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Performed at any time prior to start of study therapy

- Archival tumor sample for NCI LP confirmation of diagnosis. A block of primary tissue (or 5-10 unstained sections on charged slides) from the time of diagnosis will be required from each patient. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable. Referring institutions will send the tumor block or 5-10 unstained sections on charged slides to CCR/NCI for correlative studies and confirmation of diagnosis. A fresh biopsy or tumor effusion sample will be collected if archival tumor tissue is not available. Note: with the exception of collection of fresh biopsy, this activity is covered under the waiver referenced above and may be performed prior to obtaining consent.

Performed within 28 days prior to start of study therapy or, if applicable, second course

- History and physical exam
- Vital signs including pulse oximetry
- ECG
- Echocardiogram
- CT scan of chest, abdomen and/or pelvis and areas of known or suspected disease involvement; MRI may also be performed when appropriate. Additional imaging may be done as clinically indicated. (If patient being assessed for Second Course, please see Appendix D)
- FDG-PET scan
- Urinalysis

Performed within 10 days prior to start of study therapy or, if applicable, second course

- CBC with differential, Acute Care Panel (sodium, potassium, chloride, bicarbonate, creatinine, glucose, BUN), Hepatic Panel (alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin), Mineral Panel (albumin, calcium, magnesium, phosphorus), creatine kinase, C-reactive protein, Coagulation (PT, PTT, fibrin degradation products), lactate dehydrogenase, Thyroid (TSH, free T4, total T3)

Performed within 7 days prior to start of study therapy or, if applicable, second course

- ECOG performance status (within 7 days)

Performed within 72 hours prior to the start of study therapy or, if applicable, second course

- Urine or serum hCG in women of childbearing potential (must be repeated on C1D1 (pre-treatment) if more than 72 hours have passed since screening assessment)

## 2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

### 2.3.1 Treatment Assignment Procedures

**Cohorts**

| Number | Name | Description |
|---|---|---|
| 1 | Pleural mesothelioma | Up to 12 or up to 25 (depending on interim analysis) evaluable subjects with pleural mesothelioma |
| 2 | Peritoneal mesothelioma | Up to 6 or up to 10 (depending on interim analysis) evaluable subjects with peritoneal mesothelioma |

**Arms**

| Number | Name | Description |
|---|---|---|
| 1 | LMB-100+pembrolizumab | LMB-100 administered in cycles 1 & 2 + pembrolizumab |

| | | |
|---|---|---|
| | | administered in subsequent cycles |

**Stratifications, Randomization and Arm Assignment**

No stratification or randomization will occur on the study.

Subjects in Cohort 1 will be directly assigned to Arm 1. If 3 or more subjects among the first 12 enrolled have an objective response, 13 additional evaluable subjects will be enrolled.

Subjects in Cohort 2 will be directly assigned to Arm 1. If 1 or more subjects among the first 6 enrolled have an objective response, 4 additional evaluable subjects will be enrolled.

# 3 STUDY IMPLEMENTATION

## 3.1 STUDY DESIGN

This is an open-label, single center Phase II study of LMB-100 followed by pembrolizumab in patients with advanced pleural or peritoneal mesothelioma who have progressed on standard therapies. Patients will receive LMB-100 only at the single agent MTD, 140 mcg/kg*, on days 1, 3 and 5 of a 21-day cycle for the first two cycles. Regardless of tumor response (CR/PR, SD, PD) after LMB-100 monotherapy, if conditions in section 3.3.2.1 are met, subjects will receive pembrolizumab monotherapy (200 mg) on day 1 of each subsequent 21-day cycle for up to 2 years or until disease progression on pembrolizumab, or intolerable toxicity, whichever occurs first. Cycle 3 dosing will not be initiated until LMB-100 related toxicities have resolved to grade 1 or better; however, if the initiation of cycle 3 is delayed for more than 4 weeks, the patient will be removed from study therapy.

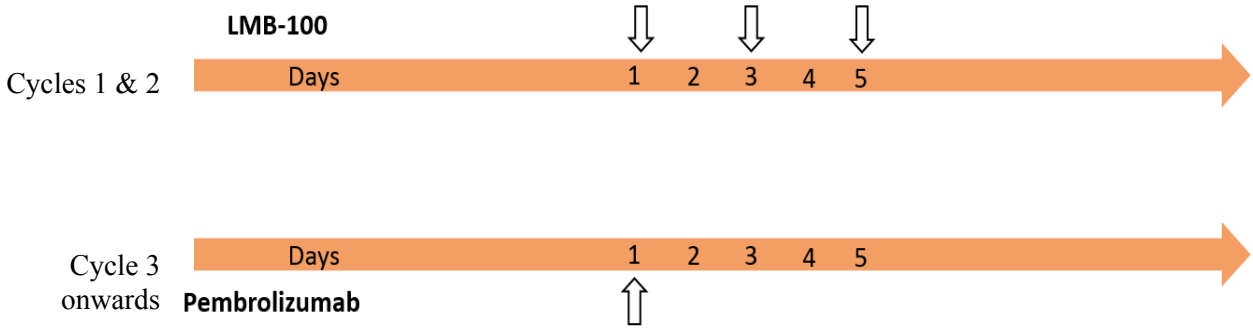
If needed a dose level below the single agent MTD of LMB-100 will be explored.

Tumor biopsies will be performed at baseline, at the end of cycle 2 and at the end of cycle 4 to evaluate changes in the tumor immune microenvironment following treatment with LMB-100 and pembrolizumab.

* Note: A weight-based dose cap will be applied. LMB-100 dose for patients weighing more than 100 kg will be calculated as if they weigh 100kg.

### 3.1.1 Schema

| |
|---|
| 3-week cycles; Response evaluation every 2 cycles; biopsy at baseline, at the end of cycle 2 and at the end of cycle 4. Pembrolizumab may continue for a maximum of 2 years. All participants who stop study treatment with stable disease or better may be eligible for an additional 17 cycles of pembrolizumab if they progress after stopping study treatment from the initial phase. |




### 3.1.2 Second Course

All participants who stop study treatment with stable disease or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

**Either**

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

**OR**

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of study treatment, and

- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the safety and efficacy endpoints of the study.

## 3.2 DRUG ADMINISTRATION

### 3.2.1 LMB-100

The qualified health care professional responsible for dispensing the study drug will prepare the correct dose according to the cohort allocation of each patient.

LMB-100 (see section 3.1 for dose) will be given as an IV solution on Days 1, 3, and 5 (QOD× 3) of a 21-day cycle for two cycles.

LMB-100 must be administered in a hospital or clinic equipped for IV chemotherapy. Full emergency resuscitation facilities should be immediately available and patients should be under close supervision of the investigator or delegate at all times.

The compatibility and stability of the active ingredient was tested under simulated preparation/administration conditions.

#### 3.2.1.1 Preparation Instructions

1. Visually inspect the LMB-100 drug product prior to dose preparation. The solution should be colorless to brownish and may contain a small amount of translucent-to white amorphous LMB-100 particulates. Do not use if other particulate matter is seen or if the study drug is discolored. Do not shake the vial to mix.
2. Use an appropriate sized syringe and needle to draw up the required volume of LMB-100 (undiluted drug) plus an additional 3 mL (overfill for priming the syringe extension line) from the vial.
3. Attach a Smiths Medical Ultra™ Small Bore Extension Set (REF #MX448HL60) to the syringe and a Smith medical 0.2 micron filter set (MX448HF) to the end of the extension set, then prime close to the distal end. Purge all air from the syringe and line. Cap with a sterile Spiro cap before dispensing.

#### 3.2.1.2 Administration Instructions

1. Intravenous (IV). Do not administer as IV push or bolus.
2. LMB-100 is administered either peripherally or centrally through a patient's vascular access device. If there is no pre-existing central vascular access device (VAD) and peripheral access is inadequate, a central access device will be installed.
3. Undiluted LMB-100 (1 mg/mL) will be transferred to a disposable syringe and administered by IV infusion using a syringe pump. LMB-100 will be diluted in-line 1:10 with 0.9% Sodium Chloride Injection, USP immediately prior to administration.
4. To accomplish this, a side flow with 0.9% Sodium Chloride Injection, USP, must be applied. A 4-way stopcock (alternatively two 3-way stopcocks joined end-to-end, or an alternative manifold with at least two inlets and one outlet ports that can be opened simultaneously) should be positioned at the patient's VAD to allow simultaneous

infusion of LMB-100 and 0.9% Sodium Chloride Injection, USP. The infusion rate of the 0.9% Sodium Chloride Injection will be 9-times the hourly rate of LMB-100.

5. LMB-100 will be filtered inline during administration with a 0.2-0.22micron filter.

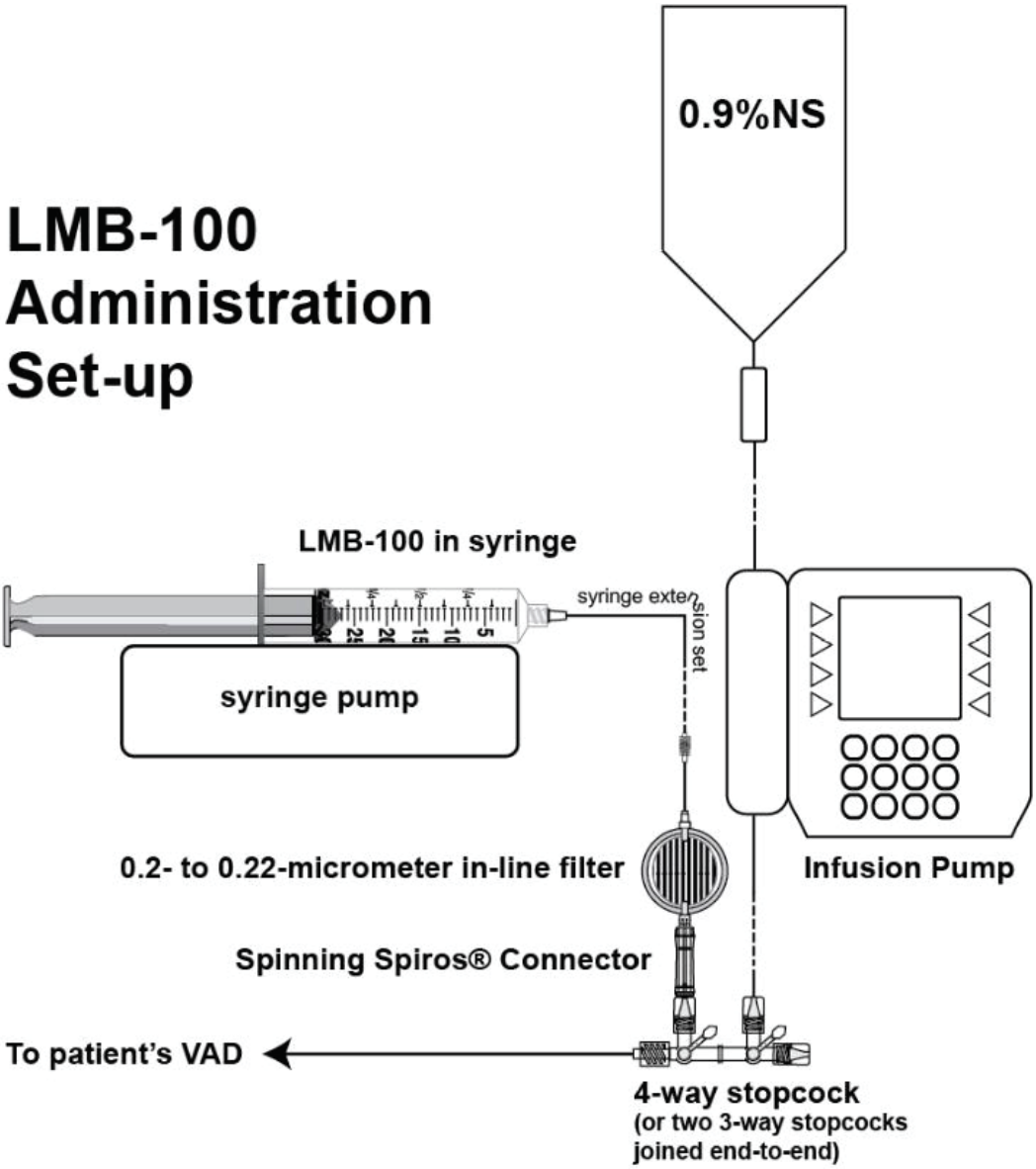



Figure 5. Schematic view of the administration set-up.

The LMB-100 drug product should be filtered using an in-line filter as depicted.

If using a peripheral IV, the IV line should remain in place for 2 hours after the end of the infusion. If no infusion related symptoms occur during this time, the infusion line may be removed. For subsequent infusions and if no IRR has been reported, the IV line should remain in place for at least 30 minutes from the end of the infusion. If no adverse events occur during the 30 minutes, the infusion line may be removed.

During infusion, vital signs (including, if possible, supine diastolic and systolic blood pressure, pulse rate, and temperature) must be monitored pre-infusion, every 15 minutes (± 5 minutes) until the end of the infusion, and thereafter, every 30 minutes (± 10 minutes) until the infusion line is removed. Vital signs during the infusion are not required to be captured in the eCRF unless abnormalities are observed.

LMB-100 drug product (DP) should be administered diluted using a side flow set-up at 1:10 (0.1 mg/mL DP). In order to not compromise drug product physico-chemical stability, the dilution with 0.9% NaCl should be done **in line**, immediately prior to administration of the DP. The infusion duration should be 30 minutes (-5 minutes, + 10 minutes); **however, the duration can be increased at the discretion of the investigator** based on the total dose and volume to be administered and the patient's physical condition. Syringe preparation and infusion duration should not exceed a maximum of 4 hours. In case of any adverse events related to the infusion, please refer to the specific recommendation described in section 3.3.1.

#### 3.2.1.3 Premedications for Patients Receiving LMB-100

Due to the prevalence of infusion related reactions (IRRs) seen in the previous study of LMB-100, all patients will be predicated 30-60 minutes (+ 30 minutes) prior to each LMB-100 administration with the following medications:

**Table 3. Premedication for LMB-100**

| | Dose (mg) | Route |
|---|---|---|
| Acetaminophen | 650 | Orally |
| Ranitidine[a] | 150 | Orally |
| Diphenhydramine[b] | 25-50 | Orally or IV |

[a] or alternative H2 blocker at an adequate dose

[b] or alternative antihistamine at an adequate dose.

(See section 3.3.1 for complete instructions on response to IRRs)

### 3.2.2 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks = 1 cycle. Pembrolizumab will be administered on day 1 (± 3 days) of each cycle starting with cycle 3 (if conditions in section 3.3.2.1 are met) for up to 2 years unless criteria for removal from therapy (3.5.1) are met. Note: As indicated in section 3.1.2, in certain circumstances the total duration of pembrolizumab treatment may exceed the 2-year limit.

Every effort will be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Pembrolizumab may be administered on an outpatient basis.

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

## 3.3 DOSE MODIFICATIONS/DELAYS

### 3.3.1 LMB-100

LMB-100 infusion may be held for up to 72 hours due to drug-associated toxicity or adverse events from other intercurrent medical conditions (such as primary cancer diagnosis) that resolve with or without medical intervention to grade 2 or less within this time frame. Toxicities for which further LMB-100 treatment should NOT be given or which are exceptions to the above guidelines are stated below in Table 4. The table also provides guideline on how to manage some toxicities anticipated with LMB-100.

**Table 4. Guidelines for Managing Specific LMB-100 Adverse Events**

| Event | Action to Be Taken |
|---|---|
| IRR/hypersensitivity reaction | If an IRR/hypersensitivity develops, the infusion of LMB-100 should be temporarily slowed down or interrupted. The patient should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment or concomitant medication may include acetaminophen, antihistamine, IV saline, oxygen, bronchodilators, corticosteroids, and vasopressors depending on the symptoms.<br><br>If the infusion is interrupted:<br>o In the event of IRR CTCAE Grade1, upon resolution of symptoms, the infusion will resume at the same rate (the rate being used at the time that the IRR occurred).<br>o In the event of IRR Grade 2 or 3, upon resolution of symptoms, the infusion will resume at one-half the previous rate. The infusion can be re-escalated to initial rate if considered well tolerated after 1 hour of infusion.<br>o In the event of IRR CTCAE Grade 3, or CTCAE Grade 4 (which may include pulmonary or cardiac events) or an anaphylactic reaction:<br>▪ The infusion must be stopped and the patient should receive aggressive treatment<br>o Patients experiencing IRR CTCAE Grade 4 or anaphylaxis must be permanently discontinued from LMB-100 treatment |

| Event | Action to Be Taken |
|---|---|
| Capillary leak syndrome | In the event of Grade ≥2 CTCAE capillary leak syndrome (medical intervention indicated):<br>o Delay LMB-100 administration until complete resolution of the event<br>o For hypotension minimize fluid resuscitation to avoid fluid overload Minimize crystalloid solutions (e.g., saline)<br>o Vasopressor support (e.g., phenylephrine) if indicated to stabilize blood pressure<br>o Administer colloidal solutions (e.g., albumin) if there is a clinically significant and persistent systolic blood pressure drop, and the patient is symptomatic, or urine output declines<br>o For pulmonary congestion provide diuretic and/or albumin treatment in case of hypoalbuminemia as appropriate<br>o Progressive shortness of breath may require in addition endotracheal intubation or drainage of a pleural effusion<br>o For oliguria and /or rising serum creatinine level delay LMB-100 if Grade C3 urine output (<10 mL/hr)<br>o Use fluids judiciously if increase in urine output is required<br>o Use dopamine if patient is unresponsive to or unable to tolerate fluids Monitor serum albumin levels prior to the LMB-100 treatment cycle<br>o In the event of Grade ≥2 CTCAE pericardial effusion (asymptomatic effusion small to moderate size), consider delaying LMB-100 administration. In the event of Grade ≥3 CTCAE pericardial effusion (effusion with physiologic consequences) stop LMB-100 treatment until full resolution |
| Inflammatory reactions to serosal membranes | o Hydrocortisone (200 mg IV) or equivalent dose of another corticosteroid as clinically indicated<br>o In the event of Grade 2 CTCAE pericardial effusion (asymptomatic effusion small to moderate size), consider delaying LMB-100 administration. In the event of Grade ≥3 CTCAE pericardial effusion (effusion with physiologic consequences) stop LMB-100 treatment until full resolution<br>o In the event of pleuritis resulting in mild to severe pleuritic pain, treat with analgesics or steroids as |

| Event | Action to Be Taken |
|---|---|
| | clinically indicated<br>o For patients who have previously experienced pleuritis consider administration of a tapering course of prednisone for 7 days starting with the next LMB-100 infusion |
| Renal Toxicity | In the event of Grade 1 or greater renal toxicity consider increasing oral or intravenous hydration, and consider delaying LMB-100 administration by up to 72 hours.<br>In the event of Grade 2 or greater renal toxicity hold LMB-100 administration until recovery to Grade 1 or better. If this does not occur within 72 hours, no further LMB-100 should be given during the cycle. |
| IRR = infusion related reaction; IV = intravenous; CTCAE = Common Terminology Criteria for Adverse Events | |

3.3.2 Pembrolizumab

3.3.2.1 Dose delays

Cycle 3 day 1 of pembrolizumab may be delayed for up to 4 weeks if LMB-100 related toxicity has not resolved to grade 1 or better. If the delay exceeds 4 weeks, the patient will be removed from study therapy.

3.3.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

**Table 5: Dose modification and toxicity management guidelines for immune related AEs associated with pembrolizumab**

**General instructions:**

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

| **Immune-related AEs** | **Toxicity grade or conditions (CTCAEv5.0)** | **Action taken to pembrolizumab** | **irAE management with corticosteroid and/or other therapies** | **Monitor and follow-up** |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• Add prophylactic antibiotics for opportunistic infections |
| | Grade 3 or 4, or recurrent Grade 2 | Permanently discontinue | | |
| Diarrhea / Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of |

| **Immune-related AEs** | **Toxicity grade or conditions (CTCAEv5.0)** | **Action taken to pembrolizumab** | **irAE management with corticosteroid and/or other therapies** | **Monitor and follow-up** |
|---|---|---|---|---|
| | Grade 4 | Permanently discontinue | | bowel perforation (i.e., peritoneal signs and ileus).<br>• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. |
| Aspartate aminotransferase / Alanine aminotransferase increased or blood bilirubin increased | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable |
| | Grade 3 or 4 | Permanently discontinue | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | |
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer anti-hyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes. |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated. | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |

| Immune-related AEs | Toxicity grade or conditions (CTCAEv5.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Hyperthyroidism | Grade 2 | Continue | • Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and Renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| All other immune-related AEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis | | |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |

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

**NOTE:**

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

**Table 6:** Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

| **NCI CTCAE Grade** | **Treatment** | **Premedication at Subsequent Dosing** |
|---|---|---|
| **Grade 1**<br>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**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines | No subsequent dosing |

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br><br>Grade 4:<br><br>Life-threatening; pressor or ventilatory support indicated | NSAIDs<br><br>Acetaminophen<br><br>Narcotics<br><br>Oxygen<br><br>Pressors<br><br>Corticosteroids<br><br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br><br>Hospitalization may be indicated.<br><br>**In cases of anaphylaxis, epinephrine should be used immediately.<br><br>**Participant is permanently discontinued from further study drug treatment.** | |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br><br>For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov | | |

#### 3.3.2.4 Other allowed dose interruption for pembrolizumab

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

## 3.4 STUDY CALENDAR

1 cycle =21 days

Screening assessments will occur within 28 days prior to start of study therapy unless otherwise indicated. If screening assessments are performed within 3 days prior to dosing, the assessments do not need to be repeated on C1D1 unless otherwise indicated.

Assessments after C1D1 may be performed up to 3 days prior to indicated time unless otherwise indicated.

LMB-100 dosing cycles after cycle 1 may be delayed for up to two weeks to accommodate schedule conflicts, Federal holidays and inclement weather, etc. Pembrolizumab dosing cycles after may be delayed up to three weeks for the same reasons; however, cycle 3 may be delayed for longer as described in section 3.3.2.1.

| Procedure | Screening | Cycles 1 & 2 | | | | | | Subsequent Cycles (for a maximum of 2 years after initial pembrolizumab therapy and, if applicable, through second course)[15] | Safety Follow-Up Visit (~30 days after completion of study therapy)[16] | Safety Follow-Up Visit (~ 90 days after completion of study therapy)[16] | Long-Term Follow Up (every 6 – 12 weeks)[17] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 | Day 4 | Day 5 | Day 8 | Day 15[14] | Day 1 | | | |
| LMB-100 | | X | X | | X | | | | | | |
| Pembrolizumab | | | | | | | | X | | | |
| History and PE | X | X | X | | X | X | X | X | X | X | |
| Weight | | X | X | | X | X | X | X | X | X | |
| Height | | X | | | | | | | | | |
| Vital signs[1] | X | X | X | | X | X | X | X | X | X | |
| Performance Score | X[2] | X | | | | | | X | | | |
| Labs[3] | X[4] | X[5] | X | | X | X | X | X | X | X | |
| Urinalysis | X | X | | | | | | X | | | |

| Procedure | Screening | Cycles 1 & 2 | | | | | | Subsequent Cycles (for a maximum of 2 years after initial pembrolizumab therapy and, if applicable, through second course)[15] | Safety Follow-Up Visit (~30 days after completion of study therapy)[16] | Safety Follow-Up Visit (~ 90 days after completion of study therapy)[16] | Long-Term Follow Up (every 6 – 12 weeks)[17] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 | Day 4 | Day 5 | Day 8 | Day 15[14] | Day 1 | | | |
| Urine albumin/creatinine ratio | | Days1-6 (+4 days if patient still in hospital) | | | | | | | | | |
| HLA Typing (Class I and Class II) | | X[6] | | | | | | | | | |
| Urine or serum hCG in women of childbearing potential[7] | X[8] | X[8] | | | | | | X | X | X | |
| Confirmation of dx[9] | X | | | | | | | | | | |
| NIH Advance Directives Form | | X[10] | | | | | | | | | |
| Biopsy (optional) | | X[6] | | | | | | C3 and C5 1st course only | | | |
| Correlative Research Studies | | Please see section 5.2 | | | | | | | | | |
| CT CAP and/or MRI[11] | X | Every2 cycles ± 7 days | | | | | | | X[12] | X[12] | X |

| Procedure | Screening | Cycles 1 & 2 | | | | | | Subsequent Cycles (for a maximum of 2 years after initial pembrolizumab therapy and, if applicable, through second course)[15] | Safety Follow-Up Visit (~30 days after completion of study therapy)[16] | Safety Follow-Up Visit (~ 90 days after completion of study therapy)[16] | Long-Term Follow Up (every 6 – 12 weeks)[17] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 | Day 4 | Day 5 | Day 8 | Day 15[14] | Day 1 | | | |
| FDG-PET | X | Every 2 cycles ± 7 days | | | | | | | X[12] | X[12] | X |
| ECG[13] | X | X | X | | X | | | X | X | X | |
| Echocardiogram | X | | | | | | | | | | |
| Adverse Events | | Monitored continuously | | | | | | | | | |
| Concomitant Medications | | Monitored continuously | | | | | | | | | |
| Telephone/email follow-up q 3 months | | | | | | | | | | | X |

1 **At screening:** heart rate, blood pressure, body temperature, pulse oximetry. **During the infusions** of LMB-100 in Cycle 1, vital signs (heart rate, blood pressure, body temperature) must be monitored pre-infusion and every 15 minutes (± 5 minutes) during the infusion and then every 30 minutes (± 10 minutes) from the end of the infusion until the infusion line is removed.

2 Performed within 7 days prior to start of study therapy

3 CBC with differential, Acute Care Panel (Na, K, Cl, CO2, creatinine, glucose, BUN), Hepatic Panel (ALP, AST, ALT, total & direct bilirubin), Mineral Panel (albumin, Ca, Mg, P), lactate dehydrogenase, creatine kinase, C-reactive protein, PT, PTT, fibrin degradation products, TSH, free T4, total T3.

4 Performed within 10 days prior to start of study therapy.

5 Only required if more than 10 days have passed since screening assessment. If eligibility criteria are not met at this timepoint, subject may not be treated.

6 May be performed after study consent is signed but prior to treatment initiation (baseline)

7 Required in women of childbearing potential (see Appendix B for definition).

[8] Performed within 3 days prior to start of study therapy. Must be repeated on C1D1 (pre-treatment) if more than 72 hours have passed since screening assessment and actual treatment initiation.

[9] Please see section 2.2 for tissue requirements

[10] As indicated in section 12.3, all subjects will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended but is not required.

[11] MRIs are only performed for clinical reasons on this study. Under those circumstances, gadolinium is used only if clinically indicated.

[12] Performed only if patient removed from study therapy for reason other than progressive disease on pembrolizumab

[13] Single 12-lead ECG will be recorded at screening, then pre- and end of LMB-100 infusion for first cycle and at the withdrawal and follow-up visit. Pre-infusion at all other study drug administrations. Additional unscheduled ECG assessments should be performed if cardiovascular symptoms or abnormalities occur.

[14] Day 15 laboratory assessments may be performed outside of NIH. History may be performed remotely, and physical exam is only required in subjects seen at NIH.

[15] Per section 3.1.2, some subjects may be eligible for up to an additional 17 cycles of therapy, called the second course. Surveillance during the second course will be the same as during the initial course unless otherwise indicated. See Appendix D for further details on second course imaging.

[16] Follow up visit will occur within +/- 1 week of indicated time. The assessments listed refer to those that will be performed if the patient is seen in clinic **(first course and second course)**. If the patient is unable to return to the clinic for the follow up visit, adverse event and ECOG assessments will be performed by telephone or email, we will request that required labs, scans and ECG evaluations be performed locally and provided to us, and if the patient has visited a local oncologist in this timeframe, the progress notes will also be requested.

[17] Scans performed only in patients who have not had progressive disease on pembrolizumab. Scans will continue every 6 weeks until disease progression or start of a new anti-cancer treatment. After disease progression on pembrolizumab or in those subjects who were removed from study therapy for reasons other than disease progression, subjects will be followed every 12 weeks by telephone/email for assessment of survival status, adverse events and initiation of new anti-cancer therapy

## 3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 90 days following the last dose of study therapy.

3.5.1 Criteria for removal from protocol therapy

- Completion of protocol therapy
    - Note: The number of treatments is calculated starting with the first dose of pembrolizumab. Participants who stop pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1.2. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Progressive disease on pembrolizumab
- Noncompliance with study treatment or procedure requirements
- Requirement for use of prohibited medications/vaccines (see 4.2)
- Recurrent Grade 2 pneumonitis
- Participant (or LAR if one was designated when participant become incapacitated during study) requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section 3.3
- Investigator discretion
- Positive pregnancy test

3.5.2 Off-Study Criteria

- Screen failure
- Investigator decision to end the study
- Participant requests to be withdrawn from study
- Study drug no longer available
- Lost to follow up
- Death

## 3.6 CLINICAL CRITERIA FOR EARLY TRIAL TERMINATION

This is a sequential study of LMB-100 followed by Pembrolizumab. The single agent maximum tolerated dose of both agents has been previously established in phase I studies. Although the half-life of LMB-100 is less than 1 hour and we do not expect any LMB-100 present in the blood when pembrolizumab is initiated (at least 16 days from last dose of LMB-100), we have put the following safety parameters in place in case pre-administration of LMB-100 increases toxicity of pembrolizumab.

If any of the following occur, enrollment of new patients will be halted until the association with treatment is fully established and mitigation strategies are put in place.

1. Any grade 5 toxicity related to treatment.

2. Any new grade 3 or 4 toxicity not previously associated with pembrolizumab.

3. Increased incidence of adverse events known to be associated with pembrolizumab

Mitigation strategies will be submitted as amendments to the FDA and IRB. Should the regulatory bodies approve the amendment, the study will resume enrollment.

# 4 CONCOMITANT MEDICATIONS/MEASURES

All concomitant medications received within 28 days before the first dose of trial treatment and 90 days after the last dose of trial treatment (first course and if applicable, second course) should be recorded. Concomitant medications administered after 90 days after the last dose of trial treatment (first course and if applicable, second course) should be recorded for SAEs and ECIs as defined in Section 7.2.

## 4.1 PERMITTED THERAPY

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.

Supportive care may be administered according to NIH CC Pharmacy Guidelines unless otherwise specified in section 3.3.

## 4.2 PROHIBITED THERAPY

Patients should be treated for all concomitant conditions and adverse events according to accepted standards of medical care at the discretion of the investigator. The following treatments are not permitted while patient is receiving study therapy:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than the study agents
- Radiotherapy. Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- 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 considered per investigator discretion.

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 study. 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.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy is required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

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

# 5 BIOSPECIMEN COLLECTION

## 5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

### 5.1.1 Pharmacokinetic Assessments

All blood samples for PK assessment will be collected from an IV line different to that receiving the infusion to measure free and total concentrations for LMB-100 for all patients. The date and time of each sample collection will be recorded. If multiple samples are drawn at a given time point, the PK sample should take precedence.

Free and total plasma concentrations of LMB-100 will be measured using validated ligand-binding assays.

#### 5.1.1.1 Sample collection:

Blood for PK samples should be drawn from the opposite extremity as the one used for drug delivery. If feasible, a peripheral line used for this purpose should remain in place until the last scheduled collection for a given day. Blood will be collected in 2 mL $K_2$EDTA tubes (purple top) at the times defined in section 5.2. Samples should be inverted 8 to 10 times after collection. Store on wet ice or at 4°C. Processing within 60 minutes of blood collection is highly preferred.

#### 5.1.1.2 Sample processing

Samples will be processed in the Clinical Pharmacology Program.

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Upon arrival in the CPP the following procedures should be followed:

1. Store on wet ice until centrifugation.
2. Centrifuge 1500xg for 10 minutes at 4°C within 60 minutes of blood collection.
3. Transfer plasma specimen to 2mL cryovials and store at -70°C.

The analyses will be performed retrospectively in batched samples or at the end of the trial.

5.1.1.3 Sample Shipping

Samples will be shipped by the CPP on dry ice to the below address for analysis.

Leidos Biomedical, Inc.
Attention: Ms. Yanyu Wang, Dr. Jon Inglefield
Building 469, Room 120
Miller Drive
Frederick, MD 21702
Phone: 301-846-6905/301-846-6865

5.1.1.4 Sample storage

Samples will be stored in the CPP until shipment to the Leidos Biomedical Inc. Lab in Frederick.

5.1.2 Assessment of anti-drug antibodies (ADAs)

5.1.2.1 Sample Collection

Samples will be per the schedule in section 5.2

Draw 2mL into $K_2$EDTA tube (purple top). Samples should be inverted 8 to 10 times after collection. Store on wet ice or at 4°C. Processing within 60 minutes of blood collection is highly preferred.

5.1.2.2 Sample Processing

Samples will be processed in the Clinical Pharmacology Program.

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Upon arrival in the CPP, each sample should be processed in the following manner:

1. Store on wet ice until centrifugation.
2. Centrifuge 1500xg for 10 minutes at 4°C within 60 minutes of blood collection.
3. Transfer plasma specimen to 2mL cryovials and store at -70°C.

Autoantibody levels will be retrospectively assessed.

5.1.2.3 Sample Shipping

Samples will be shipped by the CPP on dry ice to the below address for analysis.

Leidos Biomedical, Inc.

Attention: Ms. Yanyu Wang, Dr. Jon Inglefield
Building 469, Room 120
Miller Drive
Frederick, MD 21702
Phone: 301-846-6905/301-846-6865

5.1.2.4 Sample Storage

Samples will be stored in the CPP until shipment to the Leidos Biomedical Inc. Lab in Frederick.

5.1.3 Retrospective Analysis of Mesothelin and PD-L1 Expression in tumor tissue

IHC analysis will be performed by the Laboratory of Pathology at NCI to determine mesothelin and anti PL-L1 expression within the tumor at any time after study enrollment. Leftover tissue from archival specimens or tumor biopsies obtained at screening or from optional collections at baseline, C3D1 and C5D1 may be used for this purpose. Specimens will be used to correlate treatment response with mesothelin expression and with anti PD-L1 in exploratory analyses. Additionally, this tissue will undergo IHC staining to analyze CD4 and CD8 T-Cell subsets.

5.1.3.1 Specimen collection

Collection of optional tumor biopsies should be guided by ultrasound, CT scan, or other method according to the location of the selected lesion using a ≤ 18-gauge needle to provide cores ideally of at least 20 mm in length or equivalent size. At least 2, ideally 4 core biopsies will be obtained at each time point (baseline and after cycle 1). Fine needle aspiration and biopsy of bone lesions are not acceptable. All biopsies collected under this protocol will undergo review in the NCI Laboratory of Pathology.

5.1.4 Mesothelin and Megakaryocyte Potentiating Factor (MPF) Serum Samples

The levels of serum mesothelin as well as megakaryocyte potentiating factor, which is released into serum from the processing of mesothelin precursor protein will be assessed in order to determine correlation with therapeutic response.

5.1.4.1 Sample Collection

Samples will be obtained prior to the first LMB-100 dose in cycle 1 and at the end of treatment

All blood samples will be taken by either direct venipuncture or an indwelling venous access. At each sample collection time, blood (2mL) will be drawn into a 3.5-mL serum separator tube labeled as follows:

- Subject ID Number
- Study Number
- Time and date of collection

5.1.4.2 Sample Processing

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Upon arrival in the CPP, each sample should be processed in the following manner:

Allow blood to clot for 10 minutes and centrifuge to separate the serum within 30 minutes of collection. If unable to process within 30 minutes, then whole blood tubes may be stored upright in refrigerator (4-8°C) for up to 48 hours prior to processing. Processing of samples within 30 minutes is strongly preferred. Stability studies will establish if degradation of soluble mesothelin in whole blood during 0.5 to 48 hours is significant and therefore if the data from these samples should be included in the analysis.

Transfer the serum into two pre-labeled cryotubes and immediately freeze by placing on dry ice. Transfer frozen serum samples into a – 80°C freezer for storage.

5.1.4.3 Sample Storage

All serum samples will be stored by Dr. Figg's Clinical Pharmacology Program.

5.1.5 Gene expression-based characterization of the immune landscape before and after treatment with LMB-100 and pembrolizumab

As referenced above, optional tumor biopsies will be performed in consenting patients when deemed feasible at the following time points: before initiation of therapy (archival tissue may also be used), at the end of cycle 2 and at the end of cycle 4. We will evaluate tumor biopsies before and after treatment with LMB-100 and after treatment with pembrolizumab using a hybridization-based digital gene expression platform nCounter (NanoString Technologies). This platform allows for unbiased multiplexed quantification of RNA transcripts achieving sensitivity comparable to quantitative reverse-transcription polymerase chain reaction (Q-RT-PCR), without any enzymatic reaction involved in the process. We have expertise in the use of this technology for the characterization of purified cell subsets and for the study of the changes that occur in human tumors, as a consequence of a given treatment, using tumor core biopsy tissues. This analysis can be performed on flash frozen biopsies without any further isolation or enrichment of specific cell types.

For the present study, we will screen pre- and post-treatment samples for the expression of markers of immune cell subsets (CD3, CD8, CD4, etc.), local production of cytokines (interferon-gamma, tumor necrosis factor-alpha, etc.) and chemokines (CXCL13, CCL5, etc.), adhesion molecules and others. The purpose of this study is to characterize the molecular changes that occur within the tumors following treatment with LMB-100 and pembrolizumab. The ultimate goal is to gain a better understanding of the mechanism of action of this treatment, and to identify molecular correlates of clinical outcomes such as objective responses and/or improved survival.

In order to achieve these goals, flash frozen samples will be subjected to total RNA isolation followed by hybridization with capture and detection probes specific for 620 transcripts, including genes involved in the regulation of the immune function and markers expressed by tumor cells and tumor stroma. To cover those target transcripts, a combination of a commercially available pre-designed probe set (GX Human Immunology v2, NanoString Technologies) will be used in combination with a custom-designed code set of thirty additional targets (Panel Plus, NanoString Technologies). Hybridization complexes will be quantified using a NanoString

nCounter Analysis System, at the Genomics Core Facility of the Center for Cancer Research, NCI.

Results obtained by this approach will be correlated with data obtained from immunohistochemistry of tumor biopsies as well as with data from analysis of peripheral blood populations, for a comprehensive study of the mechanism of action of LMB-100 in mesothelioma patients.

Samples will be stored in the Laboratory of Dr. Raffit Hassan, Building 10, Room 3B51.

#### 5.1.6 Tumor Microenvironment Studies Using Multiplex Staining Technologies

As referenced above, optional tumor biopsy will be performed in consenting patients when deemed feasible at the following time points: before initiation of therapy (archival tissue may also be used) and after two cycles of therapy. Portions of the tumor tissue collected at both timepoints and stored in the Hassan lab (see section 5.1.5) will be provided to the CAT-I, the laboratory of Dr. Ronald Germain. The tissue will be analyzed for cancer associated immune biomarker alterations including the immune cell and tumor cell co-localization with confocal microscopy and histo-cytometry. The CAT-I lab will return confocal images and quantitative analyses of these images in figure format to the Hassan lab.

Samples will be coded in the laboratory of Dr. Raffit Hassan and sent to CAT-I for imaging studies using multiplex staining technologies. The code key will be retained by individuals in the Hassan laboratory and will not be provided to members of the CAT-I lab.

#### 5.1.7 Retrospective analysis of MSI status

Retrospective DNA analysis for microsatellite instability (MSI) will be performed in subjects that demonstrate either partial or complete response. The analysis will be performed by the Laboratory of Pathology at NCI to determine MSI status within the tumor once the best overall response for a participant has been determined. Leftover tissue from archival specimens or tumor biopsies obtained at screening or from optional collections referenced above may be used for this purpose.

#### 5.1.8 Mechanism of Capillary Leak Syndrome (CLS)

We hypothesize that treatment with LMB-100 damages proximal tubule cells of the kidney which then lose their ability to efficiently recycle albumin. This results in a fall in serum albumin and edema. To test this hypothesis, we will document proximal tubule damage by measuring KIM-1 in urine and document albumin loss by measuring the albumin to creatinine ratio in urine. KIM-1 levels will also be measured in blood.

##### 5.1.8.1 Sample Collection

Urine will be collected at the timepoints indicated in section 5.2

No additional samples will be collected for measurement in blood. Leftover frozen blood samples collected for other research purposes will be used.

##### 5.1.8.2 Sample Processing

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Urine samples must be frozen within 2 - 4 hours of collection.

5.1.8.3 Sample Analysis

Samples will be batched and shipped per instructions provided by the vendor and study team to Pacific Bio, a commercial laboratory, for analysis..

## 5.2 SAMPLE COLLECTION SCHEDULE

| Cycle | Day | PK (5.1.1) | ADA (5.1.2) | Tumor Sample[a] (5.1.3,5.1.5,5.1.6,5.1.7) | Serum mesothelin and MPF (5.1.4) | CLS[b] (5.1.8) |
|---|---|---|---|---|---|---|
| | | 2 mL $K_2$EDTA tube | 2 mL $K_2$EDTA tube | NA | 2 mL blood in 3.5 mL SST tube | ≥ 0.5 mL of urine |
| Screening | Screening period ± 3 days | | | X[a] | | |
| 1 | 1 | Pre-dose, EOI, 1, 2, 3, 4, and 6 hours after start of infusion | Pre-dose | X[c] | X | Pre-dose |
| | 3 | | | | | X |
| | 5 | Pre-dose and EOI | | | | |
| | 6 | | | | | X |
| | 8 | | | | | X |
| 2 | 1 | Pre-dose, EOI, 1, 2, 3, 4, and 6 hours after start of infusion | Pre-dose | | | |
| | 5 | Pre-dose and EOI | | | | |
| 3 | 1 | | X | X[c] | | |
| 5 | 1 | | | X[c] | | |
| End of Treatment[d] | | | | | X | |

a. Archival or if not available, a fresh Biopsy or Tumor Effusion (mandatory). Even if archival sample is available, patient may be asked for optional biopsy sample.

b. Except for day 1, samples may be collected ± 1 day from indicated time. Day 1 samples may be collected within 1 day prior to initial dosing

c. Optional biopsies – collected at baseline (biopsy if collected at screening can be used as baseline sample) and on day 1 ± 3 days of cycles 3 and 5.

d. Refers to the end of the first course. No additional research samples will be collected during the second course.

## 5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

### 5.3.1 Clinical Pharmacology Program

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in Labmatrix utilized by the CPP. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following OHSRP/IRB approval of an additional protocol, granting the rights to use the material or if the use is not considered to be human subjects research.

### 5.3.2 Leidos Biomedical, Inc. Lab

Blood and tissue collected during the course of this study will follow storage, handling and labeling procedures to ensure that security, confidentiality and sample integrity are maintained. All samples (blood or tissue) are tracked by distinct identification labels that include a unique patient identifier and date of specimen collection. Thus, samples will be coded, with access to the code key linking to personal data restricted to the study investigators.

All cryopreserved samples are tracked for freezer location and storage criteria. All Samples are stored in a locked freezer at -70°C according to stability requirements. These freezers are located offsite at NCI-Frederick, at the Leidos Biomedical, Inc. Lab in Frederick, MD. Samples will be

stored until requested by a researcher named on the protocol. All use and requests for use will be recorded by the Leidos Biomedical, Inc. Lab. Any unused samples must be returned.

Some samples as indicated below may be stored in monitored freezers/refrigerators in the investigator's laboratory at specified temperatures with alarm systems in place.

At the completion of this protocol, samples will remain in storage as detailed above. If additional studies are to be performed on any samples retaining patient identifiers, obtained during the conduct of this trial, access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. If specimens are to be discarded at any point, they will be disposed of in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested).

#### 5.3.3 NCI Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not placed in paraffin blocks is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

#### 5.3.4 Laboratory of Dr. Raffit Hassan

This study will follow storage, handling and labeling procedures to ensure that security, confidentiality and sample integrity are maintained. All samples (blood or tissue) are tracked by distinct identification labels generated by Labmatrix that include a unique patient identifier and date of specimen collection. Thus, samples will be coded, with access to the code key linking to personal data restricted to the study investigators.

Depending on specimen type, samples are stored in liquid nitrogen, in monitored freezers/refrigerators at either -20 or -80°C according to stability requirements or in a slide cabinet in the research Laboratory of Dr. Raffit Hassan (Building 10, Room 3B51)

#### 5.3.5 CAT-I Laboratory

The CAT-I laboratory (CAT-I) will obtain coded samples from the Hassan laboratory. Upon acquisition, members of the CAT-I laboratory will enter these samples into CEREBRO, an advanced sample labeling system that tracks each sample through every step of the workflow. To meet requirements for availability of primary data and for quality assurance checks, CAT-I will maintain a detailed inventory of the type (slide, paraffin block, tissue, frozen OCT block) and location of each sample in the laboratory. More specifically, paraffin blocks and accompanying slides will be maintained at room temperature in the CAT- I laboratory. Tissues provided by the

Hassan laboratory will be fixed, frozen, and stored in the CAT-I's -80°C freezer. The CAT-I laboratory will be locked when CAT-I lab members are not present. Unprocessed samples will be held by the CAT-I or returned to the Hassan laboratory upon their request. Finally, CAT-I will comply with requirements for annual Biospecimen Reporting at the NIH.

#### 5.3.6 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open as long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or until a subject withdraws consent for their continued use, at which time they will be destroyed. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples, provided they have an IRB-approved protocol and patient consent or an exemption from IRB review.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section 7.2.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, study day 1, through 90 days after removal from study treatment (first course and if applicable, second course) or until off-study, whichever comes first. Adverse events occurring more than 90 days after the last dose of study therapy (first course and if applicable, second course) are required to be recorded only if they are considered to be serious and related to the investigational agent/intervention.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, will be reported expeditiously per section 7.2.1.

## 6.2 DATA SHARING PLANS

### 6.2.1 Human Data Sharing Plan

**What data will be shared?**

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

**How and where will the data be shared?**

- Data will be shared through*:*
- An NIH-funded or approved public repository (clinicaltrials.gov).
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

**When will the data be shared?**

- Before publication.
- At the time of publication or shortly thereafter.

### 6.2.2 Genomic Data Sharing Plan

No large scale genomic data will be generated on this study; therefore, the NIH GDS policy does not apply.

## 6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (every 6 weeks if scanning continues beyond end of treatment). In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response. Refer to Appendix C for confirmatory scan and continued treatment instructions.

Response and progression will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) or Magnetic Resonance (MR) scans, and potentially other modalities according to standard of care.

For peritoneal mesothelioma, the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[36] will be used. 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.

For pleural mesothelioma, modified RECIST for MPM (malignant pleural mesothelioma)[37] should be used as described in section 6.3.2.

iRECIST described in section 6.3.3, based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs, will also be utilized for pleural and peritoneal mesothelioma as follows.

When the Investigator identifies radiographic progression while on pembrolizumab per RECIST 1.1 or mRECIST, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

### 6.3.1 Peritoneal Mesothelioma

#### 6.3.1.1 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:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

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, and abdominal masses (not followed by CT or MRI), are considered as 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 patient, 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.

#### 6.3.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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 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 slice thickness is 5 mm or less. If CT scans have slice thickness

greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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.

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.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient 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.[38-40] 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.[41]

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.

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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. 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.

c. 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.

6.3.1.3 RECIST version 1.1 Response Criteria

6.3.1.3.1 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 of 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).

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

6.3.1.3.2 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).

6.3.1.3.3 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 Patients 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: | Patients 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 Patients with Non-Measurable Disease (i.e., Non-Target Disease)**

| **n-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 | | |

6.3.2 Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) lesions are difficult to measure reliably.[37] Therefore, modified criteria were defined in 2004 adjusting target lesion measurements to the specific needs of this disease.

6.3.2.1 Modified RECIST Criteria for MPM

Target lesion:

Measurable at baseline and defined as tumor thickness measurements perpendicular to the chest wall or mediastinum in two positions at three separate levels on transverse cuts of CT scan. The sum of those 6 measurements define a pleural unidimensional measure. For reproducibility of lesion identification in follow up scans, cuts were taken at least 1 cm apart and close to anatomical landmarks in the thorax. Reassessments should be done at same position at the same level and by the same reader. Nodal, subcutaneous, and other measurable lesion were measured as per RECIST criteria. All unidimensional measurements were added to obtain total tumor measurement.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions with no evidence of tumor elsewhere.
- Partial Response (PR): At least a 30% decrease in the total tumor measurement
- Confirmed response (PR and CR): require a repeat scan at least 4 weeks apart
- Progressive Disease (PD): At least a 20% increase in the total tumor measurement, taking as reference the smallest sum on study (this includes the baseline sum if that is

the smallest on study). (Note: the appearance of one or more new lesions is also considered progression).

- 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.

6.3.2.2 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.

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Response for this Category Also Requires:** |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. confirmation |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. confirmation |
| PR | Non-PD | No | PR | |
| SD | Non-PD | 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 | |

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients 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.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

6.3.3 iRECIST

6.3.3.1 Assessment at Screening and Prior to RECIST 1.1 Progression

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

#### 6.3.3.2 Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Appendix C). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

#### 6.3.3.3 Assessment at the Confirmatory Imaging

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

#### 6.3.3.4 Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

#### 6.3.3.5 Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

#### 6.3.3.6 Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

6.3.3.6.1 Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

6.3.3.6.2 Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.[42]

#### 6.3.4 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).

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.

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.

#### 6.3.5 Progression-Free Survival

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression (on or after pembrolizumab) or death, whichever occurs first.

#### 6.3.6 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with partial response or complete response.

### 6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

## 7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

### 7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

## 7.2 OHSRP Office of Compliance and Training / IRB Reporting

### 7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported t per these policies.

### 7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

## 7.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

## 7.4 Data and Safety Monitoring Plan

### 7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section 7.2.1 will be submitted in the appropriate timeframes.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### 7.4.2 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

# 8 SPONSOR REPORTING CRITERIA

## 8.1 DEFINITIONS

### 8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

### 8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section 8.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 8.1.3 Events to Be Treated as Adverse Events for Manufacturer Reporting

- In addition to the above SAE criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose.

8.1.4 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.5 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.6 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.7 Overdose

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose).

8.1.8 Events of clinical interest

- an overdose of Merck product, as defined in Section 8.1.7
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

## 8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section 6.1. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

## 8.3 Reporting of Serious Adverse Events

Any AE that meets a protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in 8.2.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842.

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

## 8.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

### 8.4.1 Reported by Sponsor to Manufacturer

All events listed below must be reported within 24 hours of investigator knowledge of event to OSROSafety@mail.nih.gov.

ORSO will send all reports to the manufacturer as described below.

- All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment regardless of initiation of subsequent anticancer therapy.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation through 180 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

#### 8.4.1.1 Reporting of Overdose to Merck

If an adverse event(s) is associated with ("results from") the overdose (see section 8.1.7) of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

#### 8.4.1.2 Reporting of Pregnancy and Lactation to Merck

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

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described below.

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation through 180 days following cessation of the Merck product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

8.4.1.3 Immediate Reporting of Adverse Events to Merck

8.4.1.3.1 Serious Adverse Events and Events to Be Treated as Serious Adverse Events

Refer to sections 8.1.2 and 8.1.3 for definitions of SAE and events to be treated as SAEs respectively.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, regardless of initiation of subsequent anticancer therapy, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

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

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

8.4.1.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and are defined in section 8.1.8. These events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment regardless of initiation of subsequent anticancer therapy, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

8.4.2 Reported by Study Team to Manufacturer

- All AEs from the time of treatment allocation through 90 days following cessation of study treatment must be reported by the investigator. AEs will be reported per manufacturer's instructions.

## 8.5 REPORTING PREGNANCY

8.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (8.1.2) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of LMB-100 or pembrolizumab.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose should, if possible, be followed up and documented.

## 8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

# 9 CLINICAL MONITORING PLAN

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol,

regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 STATISTICAL HYPOTHESIS

The primary objective of this trial is to determine if LMB-100 followed by pembrolizumab is associated with an adequately high response rate in each of two separate cohorts of mesothelioma patients. This will require exceeding the response rate of pembrolizumab alone in patients who have pleural mesothelioma that have failed standard therapies, and will require identifying a modest response rate in patients with peritoneal mesothelioma.

The secondary objectives are to evaluate safety, duration of response, overall survival (OS), and progression-free survival (PFS) in all patients included in this phase II evaluation. Exploratory objectives include evaluation of a set of laboratory parameters, to be performed only if the treatment combination has a beneficial effect.

## 10.2 SAMPLE SIZE DETERMINATION

Since published data indicate that a response rate for pembrolizumab alone in patients with pleural mesothelioma who have failed standard treatments is approximately 20%, this trial will try to demonstrate if a response rate substantially more than 20% may be realized by the addition of LMB-100 in those patients.

Patients with pleural mesothelioma will be enrolled in a cohort and evaluated for response using a Simon optimal two-stage phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) to rule out an unacceptably low PR+CR rate of 20% (p0=0.20) in favor of an improved response rate of 40% (p1=0.40). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will determine the response rate in the 12 evaluable patients who are treated at the safe combination, and if 0 to 2 of the 12 have a clinical response, then no further patients will be accrued. If 3 or more of these 12 patients have a response, then accrual would continue until a total of 25 evaluable patients have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 3 to 7 patients with a response out of 25 patients, this would be an uninterestingly low response rate. If there were 8 or more of 25 (32%) who experienced a response, this would be sufficiently interesting to warrant

further study in later trials. Under the null hypothesis (20% response rate), the probability of early termination is 55.8%.

Patients with peritoneal mesothelioma have limited data on clinical responses, and will be enrolled in their own cohort and evaluated for response using a separate, small Simon minimax two-stage phase II trial design[43] to rule out an unacceptably low PR+CR rate of 5% (p0=0.05) in favor of an improved response rate of 30% (p1=0.30). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will determine the response rate in 6 evaluable patients, and if 0 of the 6 have a clinical response, then no further peritoneal mesothelioma patients will be accrued. If 1 or more of these 6 patients have a response, then accrual would continue until a total of 10 evaluable patients with peritoneal disease have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there is exactly 1 patient with a response out of 10 patients, this would be an uninterestingly low response rate. If there were 2 or more of 10 (20%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 73.5%.

It is expected that approximately 15-20 patients per year may enroll onto this trial. Thus, it is expected that 18 months may be required to enroll up to 35 evaluable patients (up to 25 with pleural disease and 10 with peritoneal disease). To allow for a small number of inevaluable patients, the accrual ceiling will be set at 38 patients.

## 10.3 POPULATIONS FOR ANALYSES

Modified Intention-to-Treat: participants who took at least one dose of study intervention will be included in analyses as described below

### 10.3.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with LMB-100. Events occurring after initiation of a second course of therapy will not be included in this analysis.

### 10.3.2 Evaluable for objective response:

Only those patients 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 response. Patients on the second course will not be included in this analysis.

## 10.4 STATISTICAL ANALYSES

### 10.4.1 General Approach

Patients enrolled in the two cohorts will have the fraction of patients responding reported along with 80% and 95% confidence intervals.

### 10.4.2 Analysis of the Primary Endpoints

Clinical responses will be analyzed by reporting the fraction of evaluable patients in each of the two cohorts who experience a response, along with 80% and 95% two-sided confidence intervals, separately by cohort.

10.4.3 Analysis of the Secondary Endpoints

Duration of response will be calculated from the date of clinical response determination until disease progression on or after pembrolizumab or last follow-up without progression on or after pembrolizumab. OS will be determined from on-study date until date of death or date last known alive. PFS will be determined from the on-study date until the date of progression on or after pembrolizumab or date of death without progression (as events) or until the date of last follow-up if not progressed (as a censored observation). All three of these measures will be calculated as probabilities as a function of time using the Kaplan-Meier method, and will be evaluated on all evaluable patients, separately by cohort, as well as for both cohorts combined if the results are sufficiently similar to permit pooling ($p>0.30$ for difference between the cohorts), with appropriate caveats if necessary.

10.4.4 Safety Analyses

Safety of LMB-100 followed by pembrolizumab will be assessed by reporting the grade of adverse events noted in each patient, and reporting the proportion with grade 3 and grade 4 adverse events. Safety data will be presented in individual listings. Summaries will also be prepared. The safety data will consist of the reporting of all adverse events, vital signs, physical examination data, and appropriate laboratory safety data.

10.4.5 Baseline Descriptive Statistics

Basic descriptive statistics on study participants will be summarized in the final publication.

10.4.6 Planned Interim Analyses

The number of patients with a clinical response after the first stage of the two-stage phase II cohort will be determined to permit the trial to accrue to the second stage.

10.4.7 Sub-Group Analyses

No formal sub-group analyses are planned.

10.4.8 Tabulation of individual Participant Data

No individual participant data tabulation will be required. Tables showing results of participants may be presented if warranted.

10.4.9 Exploratory Analyses

Patients who undergo biopsies at baseline as well as after two cycles of LMB-100 and/or two cycles of pembrolizumab will have the differences in the parameters obtained by the biopsies compared from baseline to each of the two subsequent time points, as well as between the post-LMB-100 biopsy and the post-pembrolizumab biopsy. These analyses will be done using appropriate paired tests (paired t-test or Wilcoxon signed rank test depending on the normality of the differences). All tests will be done with exploratory intent, separately by cohort, without adjustment for multiple comparisons but presented in the context of the number of tests performed.

# 11 COLLABORATIVE AGREEMENTS

## 11.1 CLINICAL TRIALS AGREEMENT (CTA)

The study agent pembrolizumab is supplied under a CTA (# 1101) with the manufacturer, Merck.

# 12 HUMAN SUBJECTS PROTECTIONS

## 12.1 RATIONALE FOR SUBJECT SELECTION

LMB-100 is a mesothelin-targeted cFP and has shown preclinical dose-dependent activity in monotherapy and/or combination in xenografts representing MSLN-positive indications (NSCLC, mesothelioma, triple negative breast cancer, gastric cancer, pancreas, ovarian, potentially other tumor indications). LMB-100 has shown synergy in laboratory models with inhibitors of the PD1 axis. Pembrolizumab is an anit-PD1/PD-L1 inhibitor. The rationale to evaluate LMB-100 with pembrolizumab in advanced/metastatic mesothelioma is to determine the effect of the addition of pembrolizumab to LMB-100 therapy. All patients meeting the criteria listed in section 2.1 are eligible for enrollment.

## 12.2 PARTICIPATION OF CHILDREN

There are no dosing or adverse event data are currently available on the use of LMB-100 with pembrolizumab in patients <18 years of age; therefore, children are excluded from this study.

## 12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 12.5), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

## 12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

### 12.4.1 Risks from Study Drugs

Patient safety will be managed by careful proactive patient selection prior to study to exclude patients at risk from study treatment due to their pre-existing conditions. During the study, safety of patients will be proactively managed by protocol-mandated physical examinations, vital signs assessments, ECGs, clinical laboratory assessments, and collection of adverse events and their assessment.

The risks of the study include those associated with study agent as discussed in section 13.

### 12.4.2 Blood Collection

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

### 12.4.3 CT Scans

In addition to the radiation risks discussed below, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

### 12.4.4 Image Guided Biopsy Collection

The risks of the research biopsies collected at baseline, on C2D1 and C4D1 include pain, bleeding and infection at the biopsy site. In addition, as the biopsies may be collected under CT guidance, subjects in this study may be exposed to radiation as discussed below.

### 12.4.5 Radiation

The study will involve radiation from the following sources:

- Up to 3 CT scans as referenced above for the collection of biopsies
- Up to 9 CT scans per year for disease assessment
- Up to 9 FDG-PET scans per year for disease assessment

Subjects in this study may be exposed to approximately 17.7 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 1.8 out of 100 (1.8%) and of getting a fatal cancer is 0.9 out of 100 (0.9%).

## 12.5 RISKS/BENEFITS ANALYSIS

Patients with advanced and/or metastatic pleural or peritoneal mesothelioma are in continuous need of improved therapy options. This is especially true for patients where no standard therapy exists such as the patient population that will be eligible for this trial. Preclinical data has demonstrated promising anti-tumor efficacy of LMB-100 in xenograft models in monotherapy and combination therapy. Laboratory studies have further demonstrated synergy with PD1/PD-L1 inhibitors. Therefore, LMB-100 + pembrolizumab may improve clinical outcome of patients with mesothelioma. A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefits of mesothelin targeted cFP for mesothelioma patients retaining the ability to consent and those who lose capacity to consent during the course of the trial outweigh the risks associated with the proposed entry-into-human trial with LMB-100 + pembrolizumab

## 12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., legally authorized representative [LAR] if participant is an adult unable to consent) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent for the optional biopsies performed on this study will be obtained at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

#### 12.6.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section 2.2.1 may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

## 13 REGULATORY AND OPERATIONAL CONSIDERATIONS

### 13.1 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 13.2 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI CCR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 13.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at NCI CCR This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

# 14 PHARMACEUTICAL INFORMATION

## 14.1 LMB-100 (IND # 152907)

### 14.1.1 Source

Initially LMB-100 on this trial was transferred to the NIH CC Pharmacy by Roche, the first manufacturer of the drug. As of Amendment H, the drug supply manufactured by Selecta Biosciences and transferred to the NIH CC Pharmacy will be utilized. Please note, the Roche supply may continue to be used until expiration, per PI/sponsor/pharmacy discretion.

### 14.1.2 Toxicity

Information in this section is based on preclinical studies with LMB-100, and clinical studies of the cytolytic fusion protein SS1-P. Patients should receive a full dose of LMB-100 unless a DLT and/or a treatment limiting toxicity is observed. In case of DLT and/or treatment limiting toxicities, treatment with LMB-100 will be stopped until resolution of toxicity to NCI CTCAE Grade $\leq 2$ hematological toxicities or Grade $\leq 1$ non-hematological toxicities. A delay of LMB-100 administration for up to two weeks of the planned schedule will be acceptable to allow for resolution of toxicity to NCI CTCAE Grade $\leq 2$ hematological toxicities or Grade $\leq 1$ non-hematological toxicities. If toxicity does not resolve to NCI CTCAE Grade $\leq 2$ hematological toxicities or Grade $\leq 1$ non-hematological toxicities and the patient is unable to resume treatment with LMB-100 after this time, no additional doses will be administered and the patient will be withdrawn from study treatment.

#### 14.1.2.1 Infusion-Related Reactions and Hypersensitivity Including Anaphylaxis

LMB-100 administration may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during or shortly after an infusion, predominantly the first infusion. Patients may also develop IgE-mediated hypersensitivity reactions to LMB-100. IRRs may be indistinguishable from an anaphylactic reaction. Patients should receive full supportive care to treat IRRs or anaphylaxis according to institutional practice. If infusion-associated signs or symptoms occur, patients should be monitored until complete resolution.

In vitro data suggest that the risk for the release of pro-inflammatory cytokines upon first administration of LMB-100 to humans is low (human whole blood assay, see section 1.2.4.3.3). Past experience with monoclonal antibodies that demonstrated a risk in the whole blood assay has shown that this risk could be effectively managed in the clinic with appropriate risk-minimization measures. The release of pro-inflammatory cytokines is believed to be partially responsible for the occurrence of IRRs.

#### 14.1.2.2 Risk of Immunogenicity and Potential Safety Impact

LMB-100 may cause the formation of ADAs. These may trigger hypersensitivity reactions or immune complex-mediated responses. The development of ADAs to LMB-100, an improved cytolytic fusion protein with a humanized targeting moiety directed against mesothelin and a de-humanized, truncated Pseudomonas exotoxin A is expected to be less likely than SS1P. Clinical trials with SS1P have led to the development of neutralizing ADAs in 75% and 88% of patients after 1 cycle of therapy, in the IV bolus and continuous infusion trials respectively.[44]

Patients will be monitored at regular intervals for the development of ADAs and cytokines. In particular, any clinical signs and symptoms suggestive of a hypersensitivity reaction and/or an immune complex-mediated reaction possibly due to ADA formation will be carefully investigated.

#### 14.1.2.3 Risk of Inflammatory Reactions to Serosal Membranes

LMB-100 administration may cause inflammatory reactions to serosal membranes including pleuritis, characterized by pleuritic chest pain, dyspnea, and hypoxia and pericarditis, characterized by precordial chest pain, congestive heart failure, hypotension, and uremia. Clinical trials with SS1P monotherapy have led to reversible pleuritis and pericarditis. Patients who develop symptoms of serosal inflammation should be closely monitored and receive standard treatments which may include corticosteroids.

#### 14.1.2.4 Risk of Capillary Leak Syndrome

LMB-100 administration may cause CLS characterized by hypotension, hypoalbuminemia, edema, weight gain, and hemoconcentration. Clinical trials with SS1P monotherapy have led to the development of reversible CLS. Patients will be monitored with frequent assessments of weight, edema, blood pressure, and serum albumin levels prior to and during treatment. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatments.

#### 14.1.2.5 Risk of Cardiac Toxicity

There may be a risk for cardiac immune-related adverse events, specifically **myocarditis**, as a rare but serious complication after treatment with LMB-100. During clinical trial 19C0128, a patient with history of intrahepatic cholangiocarcinoma arising out of primary sclerosing cholangitis, initiated C1 tofacitinib + apixaban treatment on Day 1 and LMB-100 on Day 4. The patient began experiencing fatigue and pleuritic pain symptoms on Day 5. A cardiac MRI was performed that suggested a component of inflammatory myocarditis in addition to capillary leak syndrome.

#### 14.1.2.6 Risk of Rhabdomyolysis

There may be a risk of rhabdomyolysis as a rare, but serious complication of treatment with LMB-100. A single patient on this study experienced grade 4 CPK increased, assessed as being due to a grade 2 event of rhabdomyolysis within one week of initial dose of LMB-100. This was determined by the sponsor to be related to the LMB-100.

#### 14.1.2.7 Risk of Renal Toxicity

LMB-100 administration may cause renal toxicity characterized by increased creatinine, BUN, and proteinuria. In preclinical cynomolgus monkey studies, LMB-100 has shown increases in creatinine and histological changes including regenerative and degenerative changes to the tubular epithelium. Hemolytic uremic syndrome has been reported for other cytolytic fusion antibodies in development.

Patients should be monitored with renal laboratory assessments including creatinine, BUN, and urinalysis.

#### 14.1.2.8 Injection Site Reactions

LMB-100 administration may cause adverse reactions at the infusion site characterized by pain, swelling, induration, and nodules. In preclinical NHP studies for both SS1P and LMB-100

reddening and swelling of the infusion site were noted. Patients who develop symptoms of infusion site reactions can be administered pain relieving medication (analgesic) as required, and rotation of infusion sites is recommended.

14.1.3 Handling

LMB-100 is to be handled following all hazardous precautions. There is no evidence currently available to determine the hazardous status of the product. The Clinical Center will exercise caution and categorize LMB-100 as a hazardous agent.

14.1.4 Formulation and preparation

LMB-100 drug product (20 mg/20 mL) is provided for syringe infusion as a sterile, colorless to brownish, preservative-free liquid in single-use, 20 mL vials. The nominal fill volume is 20 mL and the approximate concentration of LMB-100 recombinant fusion protein in the vials is 1 mg/mL.

14.1.5 Stability and Storage

14.1.5.1 Stability

Stability tests are ongoing for intact LMB-100 vials.

LMB-100 does not contain antimicrobial preservatives and should be used immediately after preparing into dosing syringes. If prepared dosing syringes are not used immediately, total in-use storage times of prepared syringes for infusion should not exceed 24 hours when stored under refrigeration (2°– 8°C).

14.1.5.2 Storage

Store intact vials in the refrigerator (2 – 8°C), protected from light. Do not shake and do not freeze drug vials.

LMB-100 should be protected from exposure to direct sunlight during preparation and administration.

14.1.6 Administration procedures

Please refer to section 3.2.1.

14.1.7 Incompatibilities

Pharmacodynamic drug interaction studies have not been conducted. LMB-100 is contraindicated in subjects with a history of severe allergic anaphylactic reactions to humanized, chimeric or mouse peptides/antibodies or to any components of the product.

Other drugs that require parenteral co-administration (if applicable) should be delivered via separate infusion lines and at separate infusion sites and should not be mixed with the study drug.

LMB-100 is compatible with non-DEHP, latex-free, lipid resistant, non-PVC extension sets.

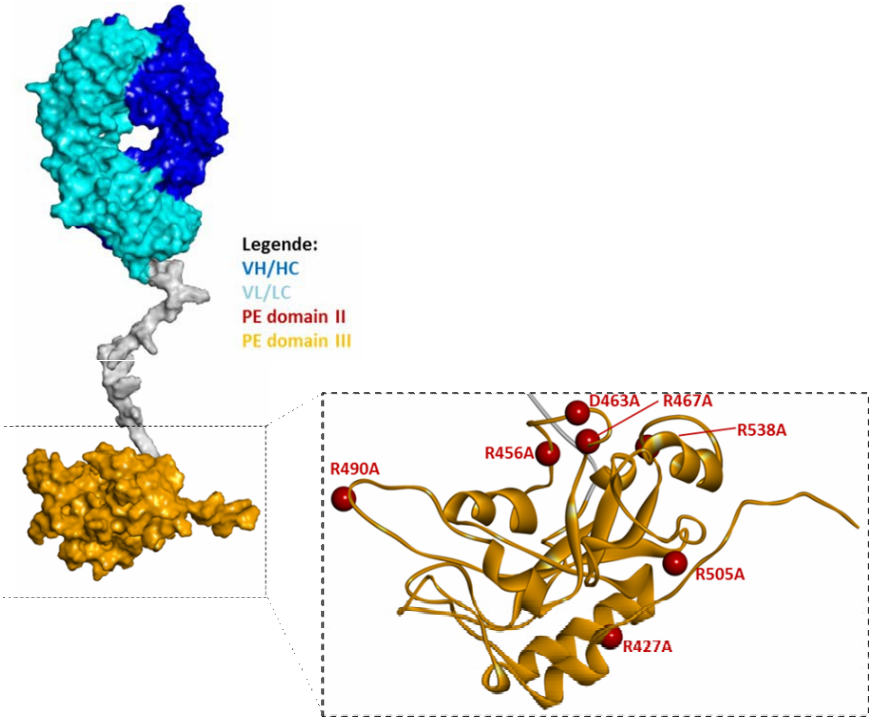
14.1.7.1 Mechanism of action

LMB-100 is a novel recombinant anti-mesothelin targeted cytolytic fusion protein (cFP) developed for the treatment of patients with solid tumors that express the mesothelin protein. Mesothelin is a suitable candidate for targeted therapy due to its very limited expression in normal/non-malignant tissue and its high expression in several tumor entities including

mesothelioma, ovarian cancer, pancreatic cancer, gastric cancer, breast cancer, and lung cancer. To target mesothelin, a humanized Fab fragment of the anti-mesothelin antibody SS1 is linked to a truncated and de-immunized recombinant 24 kD fragment of Pseudomonas exotoxin (PE24). After binding to mesothelin, the complex is internalized by endocytosis and kills cells by inhibition of eukaryotic elongation factor 2 (eEF2), leading to arrest of protein synthesis and secondarily triggering cell death by apoptosis or necrosis.

14.1.7.2 Molecular Weight: approximately 73 kDa

14.1.7.3 Chemical Structure




H1L1 polypeptide structure consisting of one variable heavy chain containing the Pseudomonas Exotoxin A moiety and one variable light change held together by a disulfide bond.

## 14.2 PEMBROLIZUMAB

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

### 14.2.1 Source

Commercially available pembrolizumab will be supplied under a CTA with the manufacturer, Merck.

### 14.2.2 Clinical Supplies Disclosure

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

### 14.2.3 Toxicity

The most frequently reported adverse events that were considered by the investigator to be "possibly," "probably," or "definitely" related to pembrolizumab are displayed below in Table 7. The 5 most frequently reported AEs considered drug related by the investigator were fatigue (24.2%), pruritus (16.7%), rash (13.8%), diarrhea (12.3%), and nausea (10.9%).

**Table 7: Most Frequently Reported ( ≥ 5%) Adverse Events Presented by Decreasing Frequency and Considered Drug-Related by the Investigator in Subjects Treated with Pembrolizumab**

| Preferred Term | Reference Safety Dataset for Pembrolizumab[a] | |
|---|---|---|
| | N | (%) |
| Subjects in population | 2799 | |
| Fatigue | 678 | (24.2) |
| Pruritus | 467 | (16.7) |
| Rash | 386 | (13.8) |
| Diarrhea | 343 | (12.3) |
| Nausea | 304 | (10.9) |
| Arthralgia | 281 | (10.0) |
| Decreased appetite | 255 | (9.1) |
| Asthenia | 218 | (7.8) |
| Hypothyroidism | 213 | (7.6) |
| Vitiligo | 159 | (5.7) |
| Myalgia | 146 | (5.2) |

Every subject is counted a single time for each applicable row and column.

MedDRA version used is 18.1.

a. Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D,

| Preferred Term | Reference Safety Dataset for Pembrolizumab[a] | |
|---|---|---|
| | N | (%) |
| C, F1, F2, F3; KN002 (original phase), KN006, and KN010. | | |

**Table 8: Serious Adverse Reactions Considered Expected for Pembrolizumab**

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| Blood and lymphatic system disorders | Anemia (NSCLC Combo Tx, UC) | | | |
| | | | | |
| | | | | |
| | Hemolytic anemia | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| Cardiac | | | | |
| | Autoimmune myocarditis | | | |
| | Myocarditis Cardiac failure (MEL) | | | |
| | | | | |
| | | | | |
| | Adrenal insufficiency | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Adrenocortical insufficiency acute | | | |
| | Autoimmune thyroiditis | | | |
| | Hyperthyroidism | | | |
| | Hypophysitis | | | |
| | Hypopituitarism | | | |
| | Hypothyroidism | | | |
| | Lymphocytic hypophysitis | | | |
| | Secondary adrenocortical insufficiency | | | |
| | Thyroid disorder | | | |
| | Thyroiditis | | | |
| Eye disorders | Autoimmune uveitis | | | |
| | Iridocyclitis | | | |
| | Iritis | | | |
| | Ocular myasthenia | | | |
| | Uveitis | | | |
| Gastrointestinal disorders | Abdominal discomfort (UC) | | | |
| | Abdominal pain (MEL, UC) | | | |
| | Abdominal pain lower (UC) | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Abdominal pain upper (UC) | | | |
| | Autoimmune pancreatitis | | | |
| | Colitis | | | |
| | Colitis microscopic | | | |
| | Constipation (MEL, NSCLC, NSCLC Combo Tx, UC) | | | |
| | Diarrhea | | | |
| | Enterocolitis | | | |
| | Enterocolitis hemorrhagic | | | |
| | Frequent bowel movements (UC) | | | |
| | Gastroenteritis (cHL, UC) | | | |
| | Nausea (MEL, NSCLC, NSCLC Combo Tx, cHL, UC) | | | |
| | Pancreatitis Oral lichen planus | | | |
| | Pancreatitis acute | | | |
| | | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Vomiting (MEL, NSCLC, NSCLC Combo Tx, HNSCC, cHL, UC)Pancreatitis necrotizing | | | |
| General disorders and administration site conditions | Asthenia (MEL, NSCLC, cHL, UC) | | | |
| | Face edema (HNSCC) | | | |
| | Fatigue (MEL, NSCLC, NSCLC Combo Tx, HNSCC, cHL, UC) | | | |
| | Generalized edema (MEL) | | | |
| | Generalized physical health deterioration (MEL) | | | |
| | Pyrexia | | | |
| Hepatobiliary disorders | Autoimmune hepatitis | | | |
| | Drug-induced liver injury | | | |
| | Hepatitis Hepatic pain (UC) | | | |
| | Hepatitis acute | | | |
| | | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Hepatitis fulminant<br>Hepatitis toxic (UC)<br>Hyperbilirubinemia (UC)<br>Liver injury (UC) | | | |
| Immune system disorders | Anaphylactic reaction | | | |
| | Anaphylactoid reaction | | | |
| | Cytokine release syndrome | | | |
| | Drug hypersensitivity | | | |
| | Graft versus host disease (cHL) | | | |
| | Hypersensitivity | | | |
| | Serum sickness | | | |
| Infections and infestations | Gastroenteritis (cHL, UC) | | | |
| | Herpes zoster (cHL) | | | |
| | Pneumonia (NSCLC, HNSCC, cHL, UC) | | | |
| | Rash pustular | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Septic shock (cHL)<br>Sepsis (UC)<br>Upper respiratory tract infection (NSCLC Combo Tx, cHL)<br>Urinary tract infection (UC)<br>Urosepsis (UC) | | | |
| Injury, poisoning and procedural complications | | | | |
| | Infusion related reaction | | | |
| Investigations | Alanine aminotransferase increased (UC) | | | |
| | Aspartate aminotransferase increased (UC) | | | |
| | Blood bilirubin increased (UC) | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Blood creatinine increased(UC)Hepatic enzyme increased (NSCLC, UC)Liver function test increased (UC)Neutrophil count decreased (NSCLC Combo Tx)Transaminases increased (UC)Weight decreased (UC) | | | |
| Metabolism and nutritional disorders | Decreased appetite (MEL, NSCLC, NSCLC Combo Tx HNSCC, UC) | | | |
| | Diabetic ketoacidosis | | | |
| | | | | |
| | Fulminant type 1 diabetes mellitus | | | |
| | Hyponatremia (UC) | | | |
| | Latent autoimmune diabetes in adults | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Type 1 diabetes mellitus | | | |
| Musculoskeletal and connective tissue disorders | Arthralgia (MEL, NSCLC, NSCLC Combo Tx, cHL, UC) | | | |
| | Arthritis | | | |
| | Back pain (MEL, NSCLC, cHL, UC) | | | |
| | Bone pain (cHL, UC) | | | |
| | Flank pain (UC) | | | |
| | Musculoskeletal chest pain (cHL, UC)Immune-mediated necrotizing myopathy | | | |
| | Musculoskeletal discomfort (cHL, UC) | | | |
| | Musculoskeletal pain (cHL, UC) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Tumor pain (UC) | | | |
| Nervous system disorders | Axonal neuropathy | | | |
| | Demyelinating polyneuropathy | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Dizziness (NSCLC Combo Tx)Diabetic ketoacidotic hyperglycemic coma | | | |
| | Dysgeusia (NSCLC Combo Tx) | | | |
| | Dysesthesia (cHL) | | | |
| | Guillain-Barre syndrome | | | |
| | Headache (MEL, NSCLC Combo Tx, cHL)Hypoesthesia (cHL) | | | |
| | Lethargy (UC) | | | |
| | Miller Fisher syndrome | | | |
| | Myasathenia gravisMyasthenia gravis crisis | | | |
| | Myasthenic syndrome | | | |
| | Myelitis | | | |
| | Neuropathy peripheral (MEL, cHL) | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Paresthesia (cHL)Peripheral sensory neuropathy (cHL)Polyneuropathy (MEL, cHL) | | | |
| Psychiatric | Confusional state (HNSCC)<br>Insomnia (NSCLC Combo Tx) | | | |
| Renal and urinary disorders | Acute kidney injury (NSCLC Combo Tx, UC)<br>Autoimmune nephritis | | | |
| | Chromaturia (UC)<br>Glomerulonephritis<br>Glomerulonephritis membranous | | | |
| | Hematuria (UC)<br>Nephritis | | | |
| | Nephrotic syndrome | | | |
| | Tubulointerstitial nephritis | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| Reproductive system and breast disorders | Pelvic pain (UC) | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| | Cough (MEL, NSCLC, NCSLC Combo Tx, cHL, UC) | | | |
| | Dyspnea (MEL, NSCLC, NSCLC Combo Tx, HNSCC, cHL, UC)<br>Dyspnea exertional (cHL, UC) | | | |
| | | | | |
| | Interstitial lung disease | | | |
| | Pneumonitis<br>Productive cough (cHL, UC)<br>Respiratory failure (HNSCC)<br>Wheezing (cHL, UC) | | | |
| Skin and subcutaneous | Acute febrile neutrophilic dermatosis | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| tissue disorders | Dermatitis | | | |
| | Dermatitis acneiform (cHL, UC) | | | |
| | Dermatitis bullous | | | |
| | Dermatitis exfoliative Dermatitis contact (cHL, UC) | | | |
| | | | | |
| | Dermatitis psoriasiform (cHL) | | | |
| | Drug eruptionDrug reaction with eosinophilia and systemic symptoms | | | |
| | Eczema | | | |
| | Eczema asteatotic (cHL, UC) | | | |
| | Erythema (UC) | | | |
| | Erythema multiforme | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Lichen planus | | | |
| | Lichenoid keratosis (UC)Palmar-plantar erythrodysesthesia syndrome | | | |
| | Pemphigoid | | | |
| | Pruritus Perivascular dermatitis | | | |
| | | | | |
| | Psoriasis | | | |
| | Rash | | | |
| | Rash erythematous | | | |
| | Rash generalized | | | |
| | Rash macular | | | |
| | Rash maculo-papular | | | |
| | Rash papular Rash morbilliform | | | |
| | Rash pruritic | | | |
| | Skin disorder | | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | | |
|---|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | | |
| | Skin hypopigmentation (MEL) | | | |
| | Skin necrosis<br>Skin reaction (UC)<br>Skin toxicity<br>Stasis dermatitis | | | |
| | Stevens-Johnson syndrome<br>Subacute cutaneous lupus erythematosus | | | |
| | Toxic epidermal necrolysis | | | |
| | Vitiligo (MEL) | | | |
| Vascular disorders | Vasculitis | rare | | |

| System/Category | **Adverse Reaction (MedDRA Preferred Terms)** | | |
|---|---|---|---|
| | **NOTE: Adverse reaction term is considered expected for *all* indications unless otherwise noted. Those terms followed by parentheses with notations afterward, are expected *only* in the indications noted.** | | |
| cHL = Classical Hodgkin Lymphoma; MEL = Melanoma; HNSCC = Head and Neck Squamous Cell Carcinoma; NSCLC = Non-Small Cell Lung Cancer; NSCLC Combo Tx = Non-Small Cell Lung Cancer participants receiving KEYTRUDA in combination with chemotherapy (pemetrexed and carboplatin); and UC = Urothelial Carcinoma For the purpose of safety reporting in clinical trials only serious adverse reactions are considered expected<br>*Term also considered expected with fatal outcome | | | |

14.2.4 Formulation and preparation

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

14.2.5 Stability and Storage

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

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

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

14.2.6 Administration procedures

Please refer to section 3.2.2.

14.2.7 Incompatibilities

None

### 14.2.8 Returns and Reconciliation

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

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

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# 16 APPENDICES

## 16.1 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. |

## 16.2 APPENDIX B: CONTRACEPTION REQUIREMENTS

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Male Participants:**

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 2.1.1.10:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

**Female Participants:**

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9 during the protocol-defined time frame in Section 2.1.1.10.

**Table 9: Highly Effective Contraception Methods**

| |
|---|
| **Highly Effective Contraceptive Methods That Are User Dependent [a]**<br>*Failure rate of < 1% per year when used consistently and correctly.* |
| ● Combined (estrogen- and progestogen- containing) hormonal contraception<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>○ Injectable |
| ● Progestogen-only hormonal contraception<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| ● Progestogen- only contraceptive implant<br>● Intrauterine hormone-releasing system (IUS)<br>● Intrauterine device (IUD)<br>● Bilateral tubal occlusion |
| ● **Vasectomized partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| ● **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) |
| Notes:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). |

## 16.3 APPENDIX C: IMAGING AND TREATMENT AFTER FIRST RADIOLOGIC EVIDENCE OF PROGRESSIVE DISEASE ON PEMBROLIZUMAB

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

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1., mRECIST = Modified RECIST Criteria for malignant pleural mesothelioma

## 16.4 APPENDIX D: SECOND COURSE (RETREATMENT) IMAGING

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Investigator assessment with site radiology reading will be used to determine eligibility.

The first on-study imaging assessment should be performed at 2 cycles ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 2 cycles ±7 days or more frequently, if clinically indicated.

Per RECIST 1.1, if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or investigator discretion, whichever occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, by the Investigator using iRECIST, in clinically stable participants.

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

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks ±7 days until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.