

Abbreviated Title: LMB-100 + Abrx in PDA
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Title: A Phase I/II Study of Mesothelin-Targeted Immunotoxin LMB-100 Alone or in Combination with Nab-Paclitaxel in Participants with Previously Treated Metastatic and/ or Locally Advanced Pancreatic Ductal Adenocarcinoma and Mesothelin Expressing Solid Tumors

NCI Principal Investigator: Christine Alewine, M.D., Ph.D.
Laboratory of Molecular Biology (LMB), CCR, NCI
Building 37, Room 5116
9000 Rockville Pike
Phone: 240-760-6146
Email: Christine.alewine@nih.gov

Investigational Agents:

Drug Name:	LMB-100 (formerly RO6927005)	Mesothelin Expression Testing
IND Number:	123332	NSR device
Sponsor/Holder:	Center for Cancer Research, NCI, NIH	Center for Cancer Research
Manufacturer:	F. Hoffman-La Roche Ltd	NCI Laboratory of Pathology

Commercial Agents

NAB Paclitaxel will be obtained from commercial sources by the NIH CC pharmacy.

PRÉCIS

Background:

- Pancreatic cancer is the fourth most common cause of cancer death in the United States, claiming more than 40,000 lives each year.
- Incidence nearly equals mortality with just 6% of participants living five years beyond their diagnosis. Most patients are diagnosed at an advanced stage, but even patients with early stage disease have a long term survival of less than 20%.
- Mesothelin is specifically a marker of adenocarcinoma in the human disease and is not expressed in preceding pre-malignant stages of tumor development
- Expression of mesothelin in pancreatic ductal adenocarcinoma (PDA) has been examined in several published studies and ranges from 86 to 100%
- Recombinant immunotoxins (RITs) are antibody-based therapeutics that carry a toxin payload. RITs that target mesothelin contain a genetically engineered variant of Pseudomonas exotoxin A (PE) in which the native cell-binding domain of PE is replaced by the mesothelin-binding antibody fragment. SS1P was the first mesothelin-targeted RIT tested in patients.
- LMB-100 contains a newly engineered PE fragment that has improved activity against most pancreatic cancer cell lines in vitro, and is also much less toxic than SS1P in pre-clinical models. The new PE contains modifications specifically designed to reduce immunogenicity of the molecule.
- Pre-administration of paclitaxel with SS1P was demonstrated to increase the amount of immunotoxin internalized by tumor cells and to reduce levels of shed mesothelin in the intra-tumoral environment so that more immunotoxin could bind tumor cells. The effect is even more pronounced with NAB-paclitaxel in a pancreatic cancer model.
- Initial clinical testing of LMB-100 was performed by Roche in a multi-center international first in human trial (NCT02317419). The agent was well tolerated and appeared to have decreased immunogenicity compared to SS1P based on preliminary results.
- In initial and subsequent clinical testing, LMB-100 was found to have half-life of ~60 mins. This is shorter than that measured for previous RITs used in the clinical setting.

Primary Objectives:

- Arm A1 (Phase I, short infusion):
 - To determine the maximum tolerated dose of short infusion LMB-100 in combination *nab*-paclitaxel chemotherapy in participants with advanced pancreatic cancer
- Arm B1 (Continuous infusion single agent lead-in):
 - To determine the maximum tolerated dose of LMB-100 given in a continuous infusion format over 24 - 96 hours to patients with advanced solid tumors that express mesothelin
- Arm B2 (Continuous infusion combination therapy):
 - Establish a tolerated dose of LMB-100 given by continuous infusion in combination with *nab*-paclitaxel chemotherapy in participants with advanced pancreatic cancer

➤ Arm A2 (Phase II, short infusion):

- To determine the objective response rate (PR+CR) according to RECIST 1.1 criteria of short infusion LMB-100 in combination with nab-paclitaxel chemotherapy in participants with advanced pancreatic cancer

Eligibility:

- Age \geq 18 years
- Histologically confirmed recurrent, metastatic and/or advanced pancreatic ductal adenocarcinoma (Except for Arm B1 [Single Agent Lead-in])
- For Arm B1 (Single Agent Lead-in), ONLY: Histologically confirmed solid tumor malignancy for which no curative therapy exists with at least 25% of tumor cells expressing mesothelin as determined by NCI Laboratory of Pathology. Determination can be made using archival tumor tissue or fresh biopsy.
- Treatment must include at least one prior chemotherapy regimen
- No nab-paclitaxel or paclitaxel treatment in the last four months (Except for Arm B1 [Single Agent Lead-in])
- Adequate organ function
- Participants with HIV, active HBV or HCV infections are eligible only for the Arm B1 (Single Agent Lead-in)

Design:

- This study is a Phase I/II open label study to assess the safety and efficacy of LMB-100 in combination with the standard of care agent *nab*-paclitaxel in participants metastatic and/or locally advanced pancreatic ductal adenocarcinoma
- Subjects will be treated for up to 2 or 3 cycles depending on arm.
- In Arm A1 (Phase I, short infusion) of the study, up to 3 dose levels will be evaluated. LMB-100 will be administered on days 1, 3 and 5 of a 21-day cycle and nab-paclitaxel will be administered on days 1 and 8
- In Arm A2 (Phase II, short infusion), if explored, up to 20 evaluable participants (including those treated at 65 mcg/kg, will be enrolled. Arm A2 will not be explored if 65 mcg/kg is not deemed safe in Arm A1
- In Arm B1 (Continuous infusion, single Agent Lead-in), escalating doses of single agent LMB-100 will be administered. The study drug will be given as a continuous infusion for the 1, 2, 3, or 4 days of a 21-day cycle.
- Arm B2 (Continuous infusion, combination therapy) will be initiated after completion of both Arm A1 and Arm B1 Single Agent Lead-in. It will test a single dose level of LMB-100 based on data from the Lead-in given in combination with nab-paclitaxel. LMB-100 will be given as a continuous infusion for 24 hours on Day 1 of a 14-day cycle. Nab-paclitaxel will also be given on Day 1.
- The Arm A2 (Phase II, short infusion) portion of the study, if explored, will be conducted in a Simon Minimax two stage phase II design. The first stage will enroll 13 evaluable participants, including the six participants treated at 65 mcg/kg. If 1 or more has a response, then accrual would continue until a total of 20 evaluable participants have been enrolled.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

1.1.1.1 Arm A1 (Phase I, short infusion):

- To determine the maximum tolerated dose (MTD) of short infusion LMB-100 when given in combination with nab-paclitaxel to participants with advanced pancreatic cancer

1.1.1.2 Arm B1 (Continuous infusion single agent lead-in):

- To determine the maximum tolerated dose of LMB-100 given in a continuous infusion format over 24 - 96 hours to patients with advanced solid tumors that express mesothelin

1.1.1.3 Arm B2 (Continuous infusion combination therapy):

- Establish a tolerated dose of LMB-100 given by continuous infusion in combination with nab-paclitaxel chemotherapy in participants with advanced pancreatic cancer

1.1.1.4 Arm A2 (Phase II short infusion):

- To determine the objective response rate (PR+CR) according to RECIST 1.1 criteria of short infusion LMB-100 in combination with nab-paclitaxel chemotherapy in participants with advanced pancreatic cancer

1.1.2 Secondary Objectives:

1.1.2.1 All Phases

- To determine the safety and tolerability of LMB-100 or the combination with nab-paclitaxel in participants with advanced pancreatic cancer
- To assess additional measures of efficacy including:
 - change in the CA 19-9 serum marker with treatment (or other appropriate tumor marker for Arm B1 [Single Agent Lead-in])
 - objective response rate (ORR) in Arms A1, B1 and B2
 - disease control rate at 4 months (as defined in section [6.3.7](#))
 - progression free survival
 - overall survival
- To define the pharmacokinetics of LMB-100 in the absence and presence of participant LMB-100 anti-drug antibodies (ADAs)

1.1.3 Exploratory Objectives:

Both phases

- To identify a threshold titer of participant LMB-100 ADAs that predicts inadequate drug exposure
- To examine the relationship between MSLN expression and response to treatment
- To identify the mechanism for Pseudomonas endotoxin-mediated capillary leak syndrome
- To examine the effect of immunotoxin treatment on the microenvironment in the Part

B portion of the study

- To determine the effect of LMB-100 on the pharmacokinetics of *nab*-paclitaxel
- To correlate plasma concentrations of nab-paclitaxel to clinical response, toxicity, pharmacogenetic analyses and pharmacodynamic endpoints
- To assess the genotype of the most relevant drug metabolizing enzymes and transporters (DMET)

1.2 BACKGROUND AND RATIONALE

1.2.1 Background on Disease

Pancreatic cancer is the fourth most common cause of cancer death in the United States, claiming more than 40,000 lives each year. Incidence nearly equals mortality with just 6% of patients living five years beyond their diagnosis. Most patients are diagnosed at an advanced stage, but even patients with early stage disease have a long term survival of less than 20%.^[1] Combination chemotherapy with FOLFIRINOX provides the greatest survival advantage for patients who have advanced disease, but the median overall survival (OS) for this regimen does not reach one year and most pancreatic cancer patients are not fit enough to tolerate it.^[2] Gemcitabine with NAB-paclitaxel is an alternative regimen and extends median overall survival to 8.5 months from 6.7 months with gemcitabine alone. The response rate (RR) to this regimen in the first-line is 23% with less than 1% of patients achieving a complete response (CR).^[3] Prospective and retrospective cohort studies have estimated a 17% RR to this regimen when given in second-line to good performance status patients following FOLFIRINOX.^[4, 5] Single agent gemcitabine remains the recommended treatment for patients with poor performance status. Erlotinib is the only targeted therapy with efficacy against this disease and extends median OS by approximately 10 days when added to gemcitabine at the expense of significant toxicity.^[6] Median survival of patients able to receive second line therapy is approximately 3-6 months.^[7] New paradigms for the effective treatment of pancreatic cancer are sorely needed.

1.2.2 Mesothelin (MSLN) as a therapeutic target

MSLN is a cell surface glycoprotein that is a differentiation antigen for mesothelial cells; expression in normal tissues is confined to the pleura, pericardium and peritoneum. The normal function of MSLN is unknown. MSLN is expressed by a wide variety of solid tumors ([Table 1](#)) Expression of MSLN in PDAC has been reported in several published studies and ranges from 86 to 100%.^[8-10] Please see [Table 2](#) below for a summary of this expression. MSLN is also expressed in tumors from genetically engineered mouse models (GEMMs) of PDAC, including the KPC model.^[11] MSLN is specifically a marker of adenocarcinoma in the human disease and is not expressed in preceding pre-malignant stages of tumor development.^[12] Increased MSLN expression in early stage PDAC participants who undergo surgical resection confers decreased survival.^[13] MSLN expression is also associated with more aggressive disease in cholangiocarcinoma, lung, ovarian and breast cancers.^[14-17] In pancreatic cancer cell lines, overexpression of MSLN increases proliferation, motility and invasion and decreases survival of mice bearing tumors grown from these cells.^[18] These properties make MSLN an attractive target for anti-neoplastic therapies, and more than five anti-MSLN agents are currently undergoing clinical testing.

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Table 1. Prevalence of MSLN expression by tumor type^[19]

Tumor Type	No. of Patients With MSLN Expression-Positive Disease (%)
Mesothelioma	290 of 352 (82)
Epithelioid	248 of 261 (95)
Sarcomatoid	0 of 23 (0)
Pancreatic adenocarcinoma	303 of 357 (85)
Epithelial ovarian cancer	346 of 494 (70)
High-grade serous	248 of 332 (75)
Endometrioid	36 of 52 (69)
Mucinous	2 of 19 (11)
Clear cell	11 of 21 (52)
NSCLC	1,157 of 2,036 (57)
Adenocarcinoma	1,082 of 1,686 (64)
Squamous	40 of 188 (21)
SCLC	0 of 55 (0)
Esophageal cancer	25 of 88 (28)
Gastric cancer	312 of 666 (47)
Biliary cancer	
Extrahepatic	93 of 98 (95)
Intrahepatic	1 of 10 (10)
Other or unspecified	36 of 85 (42)
Colorectal cancer	27 of 90 (30)
Cervical cancer	1 of 4 (25)
Endometrial cancer	34 of 58 (59)
Breast cancer	
Triple negative	33 of 50 (66)
Other	1 of 61 (1.6)
Unspecified	11 of 118 (9)

Table 2. Pancreatic ductal adenocarcinoma (5B2 antibody)^[10]

Negative	1+ (1-25% cells) [§]	2+ (26-50% cells)	3+ (>50% cells)	Total	Reference
0/60	10/60	50/60		60/60 (100%)	Argani <i>et al.</i> (5) [*]
0/14	3/14	5/14	6/14	14/14 (100%)	Frierson <i>et al.</i> (2) ^{*§}
1/11	0/11	2/11	8/11	10/11 (91%)	Ordonez (6) [*]
2/14	0/14	3/14	9/14	12/14 (86%)	Ordonez (1) [*]
7/68	22/68	39/68		61/68 (90%)	Swierczynski <i>et al.</i> (7) ^{*#}
0/18	2/18	1/18	15/18	18/18 (100%)	Hassan <i>et al.</i> (8) [*]
10/185 (5.4%)	37/185 (20%)	138/185 (75%)		175/185 (95%)	Total prevalence

^{*} 1% cutoff. [§]1+ was instead defined as focal (1-10% cells only) by Frierson *et al.* (2)

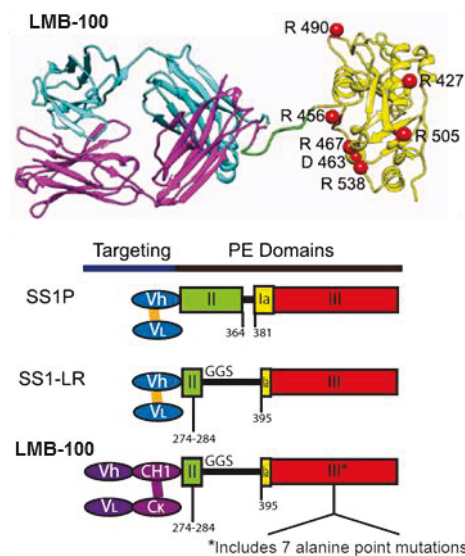
[#]Swierczynski *et al.* (7) demonstrated 10% of positive PDAC tumors could be missed in TMA versus whole sections due to focal mesothelin staining.

1.2.3 Recombinant Immunotoxins (RITs)

1.2.3.1 Mechanism and structure of RITs

RITs are antibody-based therapeutics that carry a toxin payload. RITs that target MSLN contain a genetically engineered variant of Pseudomonas exotoxin A (PE) in which the native cell-binding domain of PE is replaced by a MSLN-binding antibody fragment. In this way, the RIT binds specifically to MSLN on the cell surface and gets internalized through endocytic processes. In the cytosol, PE catalyzes an irreversible, inactivating modification of eukaryotic Elongation Factor-2 (eEF-2). This prevents the elongation step of protein synthesis, halting production of new cellular proteins, a stressor that triggers apoptosis. This mechanism of action results in cytotoxicity to both proliferating and non-dividing cells, therefore proper targeting is critical to the safety profile.^[20]

Figure 1: RIT Structure



Adapted from Alewine, *Mol. Canc. Ther.*, 13(11): 2653

Tumor-targeted bacterial toxins that inhibit the protein synthesis of cancer cells have previously shown signs of preclinical and clinical efficacy. For instance, SS1P, a classical immunotoxin format molecule derived from mouse anti-mesothelin antibody SS1 and a 38 kDa PE toxin fragment (PE38) is one example. Besides SS1P, the most clinically advanced PE-based immunotoxins are moxetumomab pasudotox, a CD22-targeted fusion protein in development by Astra Zeneca/ Medimmune, and LMB2, a CD25-targeted PE fusion protein developed by the National Cancer Institute (NCI). Both agents have shown encouraging signs of efficacy in different hematological malignancies and are currently in Phase II and III clinical trials. Denileukin difitox is the only immunotoxin approved by the US Food and Drug Administration (FDA); a fusion protein of diphtheria toxin with interleukin-2 that is clinically used for intravenous treatment of cutaneous T cell lymphoma.

1.2.3.2 Rationale for the development of LMB-100

The clinical use of SS1P, and of immunotoxins in general, has been hampered mainly by two key issues: firstly their high immunogenicity and secondly that they cause vascular leak syndrome (VLS) as a common severe side effect that is clinically difficult to manage. LMB-100 (see [Figure 1](#) for structure) is a next generation PE-fusion protein that has been protein-engineered to maximally reduce its immunogenicity and its propensity to induce VLS 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 neopeptides
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,^[21] but has also resulted in reduced incidence of VLS.^[22]

1.2.3.3 Nonclinical summary of previous generation MSLN-targeted RIT SS1P

The SS1P molecule is composed of the V_L from SS1, an affinity-matured derivative of an anti-MSLN monoclonal antibody, disulfide bonded to a fusion of V_H of SS1 with PE38. Compared to wild type toxin, the PE38 fragment lacks the cell-binding domain I (residues 1–252) as well as the toxin portion encompassing positions 365–380.

Viability of tumor cell lines expressing mesothelin is potently reduced by treatment with SS1P, resulting in half-maximal inhibitory concentration values (IC₅₀) in the single digit ng/mL range (equivalent to ~10 pM) or even lower for some tumor cell lines, while mesothelin-negative cancer cells are insensitive to SS1P even at 100 ng/mL.^[23, 24]

Using primary tumor cells from ascites or pleural effusion from nine mesothelioma patients, Zhang et al.^[25] found that in most cases mesothelin expression was lost upon in vitro culture. However, for the few samples that retained mesothelin positivity, the mesothelin level on the cell surface, which ranged from 600–200,000 sites/cell, correlated with SS1P sensitivity.

In mice, SS1P had severe off-target toxic effects on the liver, limiting the maximum tolerated dose (MTD) in a 3 × per week QOD schedule to ≤ 0.5 mg/kg.^[22] Using MTDs and the 3 × per week QOD regimen, SS1P was shown to have significant monotherapy efficacy in xenograft models of the NCI-H226 cell line (derived from pleural effusions of a mesothelioma patient).^[26] Monotherapy anti-tumor efficacy of SS1P has also been shown in xenografts of the stably transfected A431 K5 cell line,^[27] that expresses very high levels of mesothelin on the cell surface (2–5 million molecules per cell). In the same study, synergistic antitumor activity was found for the combination of SS1P with paclitaxel in vivo but not in vitro. The underlying mechanism has subsequently been claimed to be related to improved tumor penetration and intratumoral distribution of SS1P associated with a paclitaxel-mediated reduction of shedding of mesothelin from the tumor cells.^[28, 29]

When given to BALB/c mice as IV bolus injections (100 μL/mouse) at doses of 0.125 or 0.4 mg/kg, SS1P has been reported to have a serum half-life of about 26 minutes, reaching a maximum serum concentration of 3.4 μg/mL at 30 minutes post-injection. The mean residence time has been reported as 0.64 minutes and the area under the plasma concentration curve as 0.36 minutes mg/mL.^[30]

Toxicology studies of SS1P were conducted in cynomolgus monkeys with different doses and schedules, including a 1 mg/kg 3 × per week QOD schedule. Decreased appetite and physical activity was observed in animals treated with the 1 mg/kg dose level of SS1P. Necropsy studies of SS1P-treated cynomolgus monkeys showed dose-dependent, microscopic inflammation of serosal membranes, suggesting that pleuritis and/or pericarditis could be dose limiting.^[31]

1.2.3.4 Clinical Summary of previous generation MSLN-targeted RIT SS1P

SS1P has been tested in a clinical setting by the NCI in the United States.^[31] The related adverse events (AEs) included pleuritic pain, VLS, hypoalbuminemia, weight gain, fatigue, fever, and edema. In an initial Phase I trial, a cohort of 17 patients received SS1P QOD × 6 doses. The MTD was 18 µg/kg and the dose-limiting toxicities (DLTs) included Grade 3 urticaria (1 patient) and Grade 3 VLS (2 patients). To allow further SS1P dose escalation, another 17 patients were treated on a QOD × 3 doses schedule with the MTD reaching 45 µg/kg. The DLT observed was Grade 3 pleuritis (2 of 2 patients treated at 60 µg/kg and 1 of 9 patients treated at 45 µg/kg). A second trial evaluated the safety and PK profile of SS1P given as continuous infusion for 10 days.^[31] The MTD in this study was 25 µg/kg/day × 10 doses, where 1 of 6 patients had a DLT due to reversible VLS. The most common adverse events were edema (71%), hypoalbuminemia (62%), fatigue, (62%), weight gain/VLS (54%), nausea (46%), fever (46%), hypotension (38%), and allergy/rash (33%).

The clinical efficacy of SS1P in humans has been limited to date, with 4 minor responses out of 33 evaluable patients in the initial IV bolus monotherapy trial^[31] and 1 partial response out of 24 patients in the continuous infusion trial.^[31] This is most likely due to the immunogenicity of the compound, which led to the development of neutralizing ADAs in the vast majority of the patients after 1 cycle of therapy in both the IV bolus and the continuous infusion trials. This hypothesis is supported by an exploratory trial currently ongoing by the NCI in which patients are pretreated with an immunosuppressive chemotherapy regimen (pentostatin and cyclophosphamide) for 14 days prior to administration of SS1P. In this trial, 3 out of 10 patients achieved a partial response and another 3 patients achieved durable disease stabilization.^[31, 32] One of the three patients achieving a partial response did so after receiving just two cycles of SS1P before developing neutralizing anti-SS1P antibodies and coming off treatment. In addition, a recent Phase Ib study was published where SS1P was given with pemetrexed and cisplatin in advanced malignant pleural mesothelioma (MPM). SS1P was shown to be safe and well tolerated and exhibited significant antitumor activity in patients with unresectable, advanced pleural mesothelioma.^[33]

Based on the safety profile described previously for SS1P when given as single agent or in combination, the potential risks of treatment with LMB-100 were expected to include VLS, hypoalbuminemia, edema, pleuritis, infusion-related reactions, and immunogenicity. Precautions for diagnosis, monitoring, prevention, and treatment of adverse events will be provided in the Phase I studies.

1.2.4 LMB-100

1.2.4.1 Nonclinical Studies of LMB-100

1.2.4.1.1 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

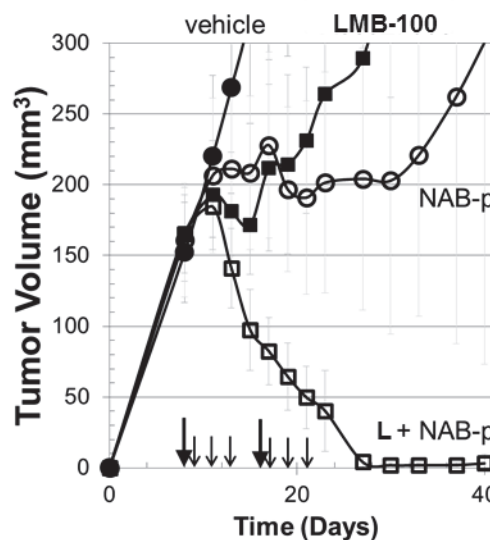
cells. In addition, control experiments showed that free PE24 was 100–1000 fold less potent on mesothelin-positive target cell lines, confirming low cytotoxic potential of PE24 lacking a targeting moiety.

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 mm³. 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 A431H9 cell line or the pancreatic cancer cell line KLM1. These results support evidence that LMB-100 may provide clinical benefit to participants with cancer.

1.2.4.1.2 Combination of taxane with LMB-100

A favorable *in vivo* interaction between paclitaxel and SS1P was first described by the Pastan lab nearly ten years ago^[27] Pre-administration of paclitaxel was demonstrated to increase the amount of immunotoxin internalized by tumor cells and to reduce levels of shed MSLN in the intra-tumoral environment so that more immunotoxin could bind tumor cells.^[28] Consistent with this mechanism, no synergy was observed *in vitro*. A similar effect has been observed with LMB-100.^[34, 35] The effect is even more pronounced with NAB-paclitaxel in a pancreatic cancer model, where all combination treated mice develop complete regressions of their tumors ([Figure 2](#)). Strikingly, the tumors never regrew in most of the animals. Similar results have been seen with in A431 cells stably overexpressing MSLN and also in tumors grown from primary mesothelioma cells. Research in our laboratory has demonstrated that this synergistic interaction can also be observed *in vitro* suggesting that a direct mechanism accounts for at least part of the effect (data not shown, manuscript in preparation). The exact mechanism remains under investigation. These data support testing of this combination in the clinic as it may have clinical benefit for pancreatic cancer patients.

Figure 2
Subcutaneous KLM1 human PDAC tumor growth in nude mice



1.2.4.1.3 Pharmacokinetics in Animals

The pharmacokinetics (PK) of LMB-100 were tested in cynomolgus monkeys following 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. Toxicokinetics 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-tumoral 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 (\pm 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.

1.2.4.1.4 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 \geq 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 \geq 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ (study day 1, preliminary data). In a subsequent 1 cycle GLP study (QOD \times 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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 VLS. 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.

1.2.4.2 Previous Roche clinical study of LMB-100

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 3](#)). Dose limiting toxicity (DLT) was reached at 250 mcg/kg, with 2 of 4 participants treated at this dose level experiencing vascular leak syndrome (grade 2 and

grade 4). Additional toxicities were associated with this toxic 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 3. 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 vascular leak syndrome and proteinuria NE, Study terminated before DLT assessment period was complete and patients only received single dose of RG7787		

1.2.4.2.1 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 vascular leak syndrome, pyrexia, atrial flutter, 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. All of 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) and rash with fever (1), 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 (see [Table 4](#) and [Table 5](#) which are adapted from Roche Final Study Report, “Summary of Adverse Events Related to Study Medication, Safety-Evaluable Patients Protocol: BP29387”). Two of four patients treated at 250 mcg/kg experienced serious VLS which manifested with hypotension, respiratory compromise, serosal membrane reaction and hyponatremia as well as the hypoalbuminemia and edema that can be seen with mild VLS. Other symptoms associated with the DLT dose were fatigue, nausea, vomiting, decreased appetite and mild elevation of transaminases. In summary, safety and tolerability of LMB-100 were as expected.

Table 4: Grade 3 or 4 Adverse Events Attributed to LMB-100¹

Dose (mcg/kg)	45	65	100	170	250	ALL
# of patients treated	1	1	3	4	4	13
Vascular leak (gr 4)	-	-	-	-	1	1
Hyponatremia (gr 3)	-	-	-	-	1	1
Anemia (gr 3)	-	-	-	1	-	1
Decreased lymphocytes (gr 3)	-	-	-	-	1	1
Dyspnea (gr 3)	-	-	-	-	1	1
Infusion-related reaction (gr 3)	-	-	1	-	-	1
Arthritis (gr 3)	-	-	1	-	-	1

¹ adapted from Clinical Study Report No 1066017 from Roche dated December 2015, “Summary of Adverse Events Related to Study Medication, Safety-Evaluable Patients Protocol: BP29387” See pages 175-193 of the report.

Table 5: Adverse Events attributed to LMB-100¹

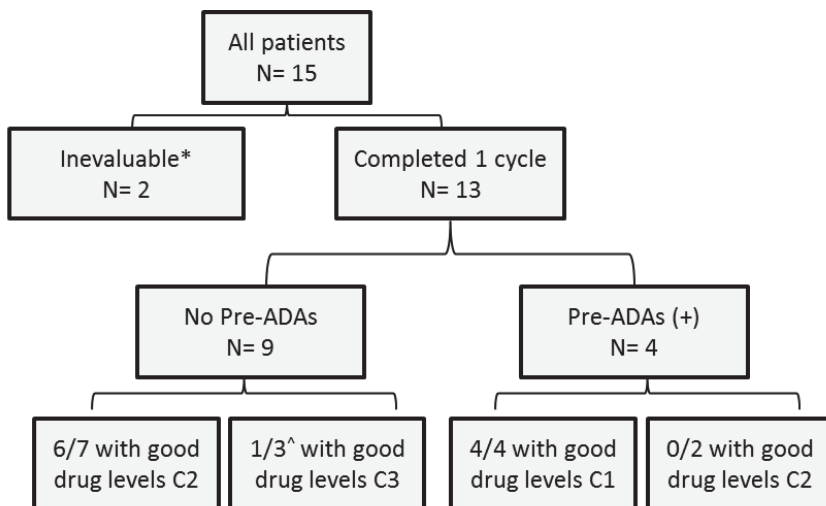
Dose (mcg/kg)	45	65	100	170	250	ALL
# of patients treated	1	1	3	4	4	13
Vascular Leak	-	-	1	1	2	4
grade 3 or 4 vascular leak	-	-	-	-	1	1
hypotension	-	-	-	-	2	2
hypoalbuminemia	-	1	3	2	3	9
peripheral edema	1	1	3	2	4	11
facial edema	-	1	2	-	1	4
weight gain	-	-	1	-	1	2
hyponatremia	-	-	-	-	3	3
hypophosphatemia	-	-	-	-	1	1
dyspnea	-	1	-	-	2	3
Infusion related reaction	-	-	2	-	2	4
Constitutional						
fatigue	-	-	-	1	4	5
asthenia	-	-	3	-	-	3
fever	1	-	2	1	2	6
Musculoskeletal						
myalgia	-	-	1	1	2	4
arthralgia	1	-	-	-	1	2
arthritis	-	-	1	-	-	1
muscle spasm	-	-	-	1	-	1
Cardiac						
pericardial effusion	-	-	-	-	1	1
Atrial flutter	-	-	-	1	-	1

Dose (mcg/kg)	45	65	100	170	250	ALL
# of patients treated	1	1	3	4	4	13
Renal Disorders						
glomerulonephritis minimal proteinuria	-	-	-	1	-	1
Creatinine increase	-	-	-	-	2	2
Gastrointestinal						
decreased appetite	-	1	-	1	2	4
nausea	1	-	1	1	4	7
abdominal pain	-	1	-	1	1	3
diarrhea	1	-	1	-	-	2
vomiting	-	-	-	-	2	2
abdominal distension	-	1	-	-	-	1
constipation	-	-	-	1	-	1
dyspepsia	-	-	-	1	-	1
AST increase	-	-	-	-	2	2
Hematologic						
anemia	-	-	-	1	-	1
decreased lymphocytes	-	-	-	-	1	1
Total Grade 3 or greater	-	-	2	1	2	5
<p>Orange highlighting indicates that one of the patients experienced a grade 3 or 4 toxicity in this category. Please note that there was only 1 patient who experienced a high grade toxicity of each type.</p> <p>¹ adapted from Clinical Study Report No 1066017 from Roche dated December 2015, “Summary of Adverse Events Related to Study Medication, Safety-Evaluable Patients Protocol: BP29387” See pages 175-193 of the report.”</p>						

1.2.4.2.2 Anti-Drug Antibodies (ADAs) and LMB-100 Drug Levels

Twelve participants were evaluable for efficacy. The best confirmed overall response was stable disease in 3 participants. A Roche-developed ELISA test was used to retrospectively assess anti-drug antibody (ADA) titers. 5 of 15 participants had detectable ADAs at study enrollment while the remaining participants did not, however, the remaining participants developed detectable ADAs by the end of Cycle 2. Immunogenicity of LMB-100 did affect serum drug levels. These data are summarized in [Figure 3](#). All evaluable participants achieved expected serum drug levels during the first cycle of treatment. Six of 7 participants without pre-existing ADAs achieved effective drug levels during the second cycle, while 0 of 2 participants with pre-existing ADAs did. One of 3 participants that received a third cycle of treatment also achieved effective drug levels during this cycle. A positive test for ADAs did not definitively predict poor blood levels in the subsequent cycle (see patient 1101 in [Table 7](#)). In summary these data show that the presence of ADAs is not predictive of ability to achieve measurable LMB-100 concentration in the serum, which is the most important parameter for drug efficacy.

Figure 3: LMB-100 ADAs and Blood Levels



*Roche closed the study before these patients completed their first treatment cycle

^One additional patient has no C3 PK data in the record but is recorded as not having progression until C4D1

Table 6: LMB-100 drug levels and ADAs in patients WITH pre-existing ADAs

Patient	Dose (mcg/kg)	Cycle 1		Cycle 2		
		ADA (Day1)	Cmax (ng/ml)	ADA (Day1)	Cmax (ng/ml)	dC1/dC2 (%)
1001	45	2700	620	196830	0	-100
1201	100	8100	495	196830	0	-100
1501*	250	2700	3730	196830	-	-
1003	250	900	2960	196830	-	-

* Patient's treatment stopped due to study closure

Table 7: LMB-100 drug levels and ADAs in patients WITHOUT pre-existing ADAs

Patient	Dose (mcg/kg)	Cycle 1		Cycle 2			Cycle 3		
		ADA (Day1)	Cmax (ng/ml)	ADA (Day1)	Cmax (ng/ml)	dC1/dC (%)	ADA (Day1)	Cmax (ng/ml)	dC1/dC (%)
1002	65	0	1150	8100	711	-38	-	-	-
1401*	100	0	1790	0	1610	-10	24300	267	-85
1402	100	0	1650	0	1360	-18	8100	0	-100
1101*	170	0	2760	300	3950	43	900	3490	26
1202	170	0	3040	0	1940	-36	-	-	-
1301	170	0	3430	72900	527	-85	-	-	-
1403	170	0	1930	900	1550	-20	-	-	-
1102*	250	0	5480	0	4770	-13	-	-	-
1302	250	0	4340	-	-	-	-	-	-

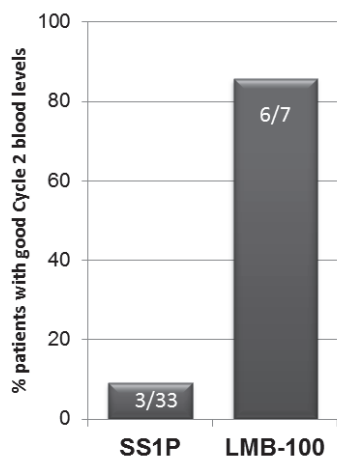
* Patient's treatment stopped due to study closure

ADA data are from Roche "Bioanalytical Report (ADA) for Clinical Study BP29387" with ADA time point codes translated as specified in the BP29837 Lab Manual Version 1.0. C_{max} data were taken from the Roche final study report.

1.2.4.2.3 Comparison of toxicity and immunogenicity of LMB-100 to SS1P

In the Roche Phase 1 trial, LMB-100 was safely administered to four patients at 170 mcg/kg without DLT. This is nearly four times the maximum tolerated dose (MTD) of SS1P. Most patients without pre-existing ADAs were able to achieve effective drug levels of LMB-100 for 2 cycles, unlike what has been seen previously with SS1P (see [Figure 4](#)). These data demonstrate that LMB-100 is both less toxic and less immunogenic than SS1P.

Figure 4: LMB-100 vs SS1P^[31] Cycle 2 Blood Levels



$p > 0.001$ by two tailed Fisher's exact test

1.2.4.3 NCI Phase I study of LMB-100 in patients with malignant mesothelioma

Clinical testing of LMB-100 in a second single agent study has recently been completed. In this trial, LMB-100 given by short infusion dosing was assessed in 10 patients with malignant mesothelioma (NCT02798536). Doses of 170 mcg/kg and 140 mcg/kg given as a 30-120 minute infusion every other day x3 doses were tested. Reversible renal toxicity that prolonged hospitalization was observed at the 170 mcg/kg dose. Therefore, **single agent short infusion MTD of 140 mcg/kg was established**. Toxicities and peak drug levels have thus far been similar to what was seen in the completed Roche study. Low serum LMB-100 levels and a high rate of infusion-related reactions were observed after cycle 2, presumably due to the development of anti-LMB-100 antibodies.

1.2.4.4 Results in current study (16C0128 as of 16 July 2018)

Part A – short infusion

As of 7/16/2018, 14 subjects have been enrolled to receive escalating doses of LMB-100 in combination with a fixed dose (125 mg/m²) of nab-paclitaxel. LMB-100 was administered on days 1, 3 and 5 of a 21-day cycle, while nab-paclitaxel was administered on days 1 and 8. Six subjects

received LMB-100 at dose level 1 (100 mcg/kg), of whom five were evaluable. Of the five, two experienced DLTs of grade 3 myalgia. Therefore, per dose escalation rules, the next LMB-100 dose level evaluated was 65 mcg/kg (dose level -1). Eight subjects have been enrolled, two of whom are deemed inevaluable. One of the six evaluable subjects experienced DLT of grade 3 edema related to LMB-100 vascular leak.. This arm of the study (Arm A1) is now completed and closed to further accrual. Dose Level -1 is the recommended Phase 2 dose. Arm A2 has opened to accrual of patients at this dose and schedule.

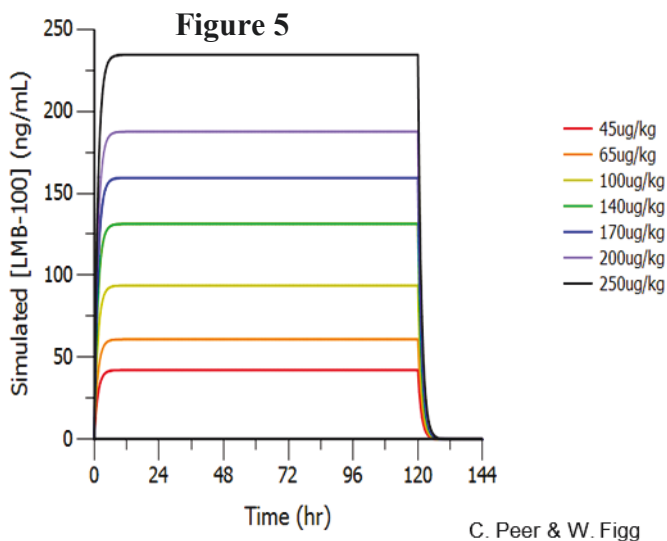
Part B – continuous infusion

Subjects are being evaluated on Arm B1, dose exploration for continuous infusion LMB-100 monotherapy. Dose level 1 was discarded after treatment of 3 patients due to erratic PK results. 1 of 6 patients at dose level 2 experienced DLT (grade 3 proteinuria). However, a planned dose de-escalation was initiated to try to determine a better tolerated schedule since 3 of 6 patients at dose level 2 experienced non-DLT VLS resulting in >5 kg weight gain. As of 7/16/18, 6 participants have been treated at dose level 3 and completed the DLT period. None of the participants experienced significant VLS. 3 of the 6 participants received on the Day 1 and not the Day 4 dose of LMB-100 due to complications from their disease unrelated to study drug (question of partial small bowel obstruction, fever and hypotension from cholangitis, dehydration from nausea and vomiting due to overeating), and were therefore inevaluable. 1 of the 3 evaluable participants did not receive the Day 4 dose of LMB-100 due to transient grade 2 creatinine elevation that was attributed at least partially to study drug. This was considered an investigator-determined DLT since the patient was unable to receive the full course of treatment due to a study-drug related toxicity.

1.2.5 Pharmacokinetics of LMB-100 and modeling of continuous infusion

The initial Roche trial demonstrated that LMB-100 has an unexpectedly short drug half-life of 61 minutes as compared to 466 minutes for the predecessor drug SS1P.^[36] It is not known what factors contribute to the longer half-life in circulation of SS1P. Using these clinical pharmacokinetic data, estimations of individual pharmacokinetic parameters that would be achieved with a continuous infusion format can be calculated (see [Table 8](#)). Using a one compartment population PK model, it is estimated through simulations that steady state maximum plasma concentration will be reached by 7 hours and that drug concentration will remain at this plateau level until the infusion is stopped ([Figure 5](#)).

Peak plasma drug concentration (C max) using the continuous infusion is expected to be 92% lower than those seen following short infusion of the same amount of drug. Following completion of the continuous infusion, drug levels are expected to fall to near zero within 5 hours from the end of infusion. Results from patients enrolled onto the first Level of the Arm B1 Single Agent Lead-in have confirmed Cmax at or lower than that



predicted by the model and also that drug levels fall to near zero in less than 4 hours from the end of infusion.

Table 8. LMB-100 drug exposure comparison

Bolus Infusion (actual)			Continuous Infusion (simulated)		
Dose (ug/kg/day)	Cmax (ng/mL)	AUC0-24 (hr*ng/mL)	Dose (ug/kg/day)	Cmax (ng/mL)	*AUC0-24 (hr*ng/mL)
45	598	674	45	42.2	957
65	1100	2245	65	61.0	1382
100	1431	2341	100	93.8	2126
140	1214	2309	140	131.3	2978
170	2406	3921	170	159.5	3615
200	2435	4342	200	187.6	4253
250	4311	6706	250	234.5	5317

*Simulated AUC0-24 was a single day's exposure during a simulated 5-day CIVI

1.2.6 Rationale for treating pancreatic cancer patients with LMB-100 and NAB-paclitaxel combination

LMB-100 targets the cell surface antigen MSLN and is ineffective against tumor or normal cells that lack MSLN. Expression of MSLN in pancreatic adenocarcinoma has been examined in several published studies and ranges from 86 to 100%,^[8-10] making this tumor type a good target for LMB-100. There is clearly an unmet need to identify improved therapies for this patient population as patients with metastatic pancreatic cancer have a median OS of less than one year with the best currently available therapies. Pre-clinical studies have demonstrated that combination of LMB-100 with nab-paclitaxel results in synergistic anti-tumor efficacy. NAB-paclitaxel is part of an FDA approved regimen for patients with advanced pancreatic cancer and addition of LMB-100 to nab-paclitaxel may improve outcomes for these patients. Given the overall poor prognosis of these patients, the potential to directly benefit from treatment with the combination regimen outweighs the risks of participating in the study.

1.2.7 Rationale for assessing continuous infusion of LMB-100

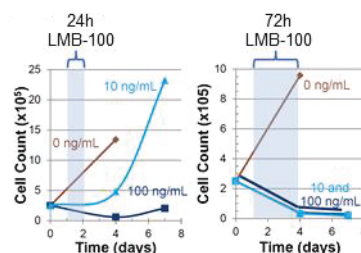
Clinical trials have shown that LMB-100 has a short half-life in humans of only 1 hour. Drugs with short half-lives can be administered by continuous infusion in order to improve drug exposure. Short half-life standard of care chemotherapies such as 5-FU and cytarabine are preferentially administered in this format. In the case of 5-FU the continuous infusion is preceded by a single bolus dose. Short half-life protein based therapeutics also appear to benefit from continuous infusion. For example, the dual specificity CD19/ CD3 bispecific T cell engaging (BiTE) antibody construct, blinatumomab, has a half-life of just over 2 hours. In initial clinical trials using a 2-4 hour infusion given 2-3 times per week, the drug performed poorly and these

trials were terminated early due to poor risk to benefit ratio.^[37] Subsequently, the drug was reintroduced in a continuous infusion format. Decreased toxicity and significant efficacy, including complete remissions in patients with chemotherapy-refractory disease, were observed.^[38] Blinatumomab has since been approved by the FDA for administration in the continuous infusion format.

We hypothesize that sustained infusion of LMB-100 will be safer and more effective than short infusion. We expect LMB-100 toxicity to decrease when given in the continuous infusion format because peak drug levels (C_{max}) will be lower and this should reduce non-specific toxicity from the drug. We expect greater efficacy because pre-clinical data suggest that duration of exposure to LMB-100 rather than peak dose may be more important for killing tumor cells. Specifically, we have found that sustained exposure of cultured cells to lower doses of LMB-100 can be more cytotoxic than treatments with higher doses given for shorter durations (Figure 6). In addition, previously published studies in mouse models with another short half-life immunotoxin demonstrated that continuous infusion of immunotoxin administered by means of surgically inserted intraperitoneal osmotic pump is less toxic; continuous infusion of these immunotoxins at MTD resulted in at least 2.5 times higher AUC than could be achieved safely with a short infusion at MTD. Because of this, better anti-tumor efficacy was achieved with the continuous infusion dosing.^[39]

Instability of LMB-100 at 37°C precludes the ability to directly test its efficacy when administered continuously for several days in mouse pre-clinical tumor models. This is because the drug must be administered in a pump kept within the peritoneal cavity at mouse body temperature throughout the experiment and the drug loses activity within 24 hours when stored at these temperatures. However, preliminary data from pre-clinical studies performed by the LMB Immunotoxin group have shown increased efficacy and decreased toxicity when using 1) intraperitoneal continuous delivery of a related short half-life MSLN-targeted immunotoxin that is stable at 37°C and 2) bolus dosing of a long-half-life anti-MSLN immunotoxin that contains an albumin-binding domain that prolongs half-life. Both studies demonstrated increased anti-tumor efficacy compared to bolus dosing of LMB-100 (Figure 7).

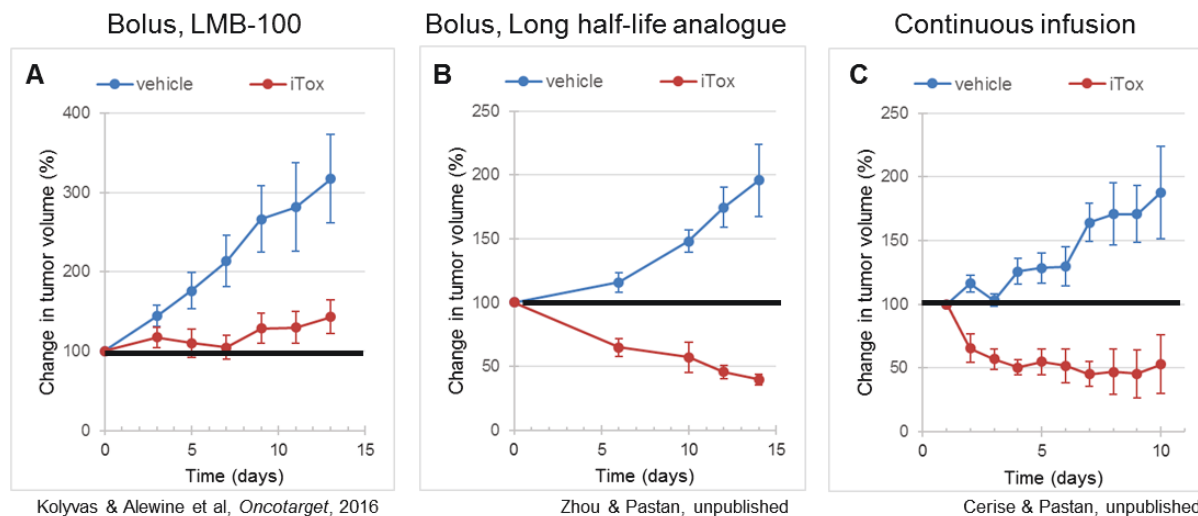
Figure 6



Longer LMB-100 exposure results in better cell kill at lower drug concentrations in KLM1 pancreatic cells.

Kolyvas & Alewine et al, *Oncotarget*, 2016

Figure 7



Athymic nude mice bearing subcutaneous KLM1 human pancreatic cancer xenografts were treated with: **A)** bolus doses of LMB-100 (50 ug, qod x3), **B)** bolus doses of an LMB-100 analogue bearing an albumin-binding domain to increase drug half-life (10 or 15 ug qday x3), or **C)** continuous dosing by surgically implanted intraperitoneal pump of mesothelin-targeted immunotoxin SS1-LR which has a half-life similar to LMB-100 but is stable at mouse body temperature. While bolus exposure to immunotoxin (iTox) in A can hal tumor growth, continuous exposure of tumors to immunotoxin (iTox) in B and C shrinks tumors by 50% or more after 1 cycle of treatment.

Continuous infusion dosing of the LMB-100 predecessor drug, SS1P, has been examined in a Phase I clinical trial. Although the long half-life of SS1P is expected to lessen the clinical impact of switching from short to continuous infusion format, these data also support our hypothesis. As predicted by the preclinical modeling, using a continuous infusion format allowed patients to achieve a higher total drug exposure. At MTD, continuous infusion resulted in an AUC of 1800 mcg min/ mL^[40] as compared to 590 mcg min/mL with the short infusion.^[36] Unfortunately, comparative efficacy of the two formats could not be adequately assessed since the immunogenicity of SS1P prevented effective dosing over multiple cycles. Since multiple cycles of LMB-100 can be administered to most patients prior to the development of anti-drug antibodies, this provides an ideal opportunity to determine whether a continuous infusion format can improve therapeutic window in the clinic as predicted by pre-clinical models.

Continuous LMB-100 will be delivered at a slow rate, i.e. which may be less than one mL per hour in some cases. The FDA has issued a warning regarding such low infusion rates particularly pertaining to high risk or life-sustaining therapies. However, LMB-100, is not considered to be a high risk (based on the fact that patients are currently tolerating infusions given over 30-60 minutes) or life-sustaining therapy.

1.2.8 Rationale for the initial dose and schedule and subsequent dose escalation of continuous infusion LMB-100

Continuous infusion of 96 hours was deemed to be the optimal duration for infusion after taking into consideration feasibility of administration and the potential risk to participants from

deconditioning while in hospital receiving continuous infusion of study drug, balanced against the possibility for increased efficacy with longer exposure times.

As outlined in section [1.2.5](#) existing clinical PK data were used to generate a model that could simulate PK parameters during continuous infusion of LMB-100. This model predicts that continuous infusion of the same dose of LMB-100 over each 24 hours by continuous infusion as compared to daily bolus dosing would result in similar total LMB-100 exposure levels but much lower C_{max} . Lower C_{max} should result in decreased off-target toxicity (such as VLS), and our pre-clinical data suggest this should not adversely affect efficacy. The effect of lower C_{max} on on-target off-tumor toxicities (such as serosal membrane irritation) is not predictable, although increased on-target off-tumor toxicity was not apparent during clinical trial using a continuous infusion format of a predecessor mesothelin-targeted immunotoxin.^[40]

Taking potential risk for increased on-target off-tumor toxicity into consideration, a reduction in starting dose compared to short-infusion MTD will be used. A dose of 65 mcg/kg was chosen as the initial dose for the escalation because it had been a) previously tested in the short infusion format in the Roche study of single agent LMB-100, and b) would also result in participants receiving ~60% less drug per cycle compared to short infusion LMB-100 given at the MTD of 140 mcg/kg every 48 hours for 3 doses (19.5 mg/ cycle versus 31.5 mg/cycle). Based upon our simulations, we predict that participant drug exposure during a 96-hour continuous infusion of 65 mcg/kg/day of LMB-100 will be 80% of that compared to patients who receive short-infusion LMB-100 given at MTD (5528 versus 6927 hr*ng/ml/ cycle). Subsequent dose levels administering 100, 140 and 200 mcg/kg/day over 96 hour continuous infusion were included although simulated drug exposures will exceed that of the short infusion MTD because the unacceptable toxicities seen with short-infusion LMB-100 at dosages higher than the established MTD for this format (VLS and reversible acute kidney injury which prolonged hospitalization) are off-target toxicities, and likely to be minimized by the lower C_{max} that is predicted with continuous infusion.

Although 96 hours is considered the optimal duration for continuous infusion, initial dose levels will test continuous infusions of 65 mcg/kg/day of drug for shorter durations since simulated drug exposure over each 48 hours of continuous infusion at 65 mcg/kg/day is 20% higher than for the short infusion MTD (2764 versus 2309 hr*ng/mL/48hr). This is because just one dose of LMB-100 is given over 48 hours in the short infusion format.

A loading dose of 40 mcg/kg LMB-100 given over 30-180 minutes will be administered prior to initiation of the continuous infusion beginning after Level 1. The loading dose is expected to improve efficacy by reducing tumor site barrier effect. Such affect has been observed in pre-clinical studies and may impair access of LMB-100 to the tumor during continuous infusion.

1.2.9 Rationale for use of mesothelin testing (NSR device)

In order to be eligible for the Arm B1 lead in portion of the study, participants are required to have positive mesothelin expression in archival tumor tissue, defined as at least 25% of tumor cells expressing mesothelin. Mesothelin expression testing is not FDA approved for this purpose; however, it is being used as an in-vitro diagnostic device. According to 21 CFR 812.3(m), a significant risk device presents a potential for serious risk to the health, safety and welfare of a subject and meets the significant risk criteria listed in the table below along with the sponsor's

conclusions with regard to the applicability of these criteria to the current study. The device has been assessed by the sponsor as non-significant risk per the below.

Significant Risk Criteria	Applicable to current study	Justification
Is an implant	No	The mesothelin test is not introduced into the subject
Is used in supporting or sustaining human life	No	The device is diagnostic
Is of substantial importance in diagnosing mitigating or treating disease or preventing impairment of human health	No	While the device is diagnostic, we do not believe in presents a potential for serious risk to the health and welfare of the subject. The assessment of mesothelin positivity is only used in tumors that may not have a high rate of mesothelin expression, and is assessed to help to increase the possibility that all persons enrolling on the study might derive benefit from therapy. Persons that are deemed ineligible to enroll on the basis of this test are eligible for studies within TGMB that are not reliant on this test.
Otherwise poses a risk	No	Testing will be performed on archival samples or on fresh tissue that is collected at screening for confirmation of diagnosis. No additional collection of tissue will occur for purposes of mesothelin testing.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- 2.1.1.1 For participants who will be receiving nab-paclitaxel (all arms except Arm B1 Single Agent Lead-in)
 - 2.1.1.1.1 Histologically confirmed recurrent, advanced or metastatic pancreatic ductal adenocarcinoma as determined by NCI Laboratory of Pathology.
 - 2.1.1.1.2 No treatment with paclitaxel or nab-paclitaxel within 4 months prior to initiation of study therapy
 - 2.1.1.1.3 ECOG performance status (PS) 0–1 ([Appendix A](#)).

- 2.1.1.1.4** Adequate hematological function: neutrophil count of $\geq 1.0 \times 10^9$ cells/L, platelet count of $\geq 95,000/\mu\text{L}$, hemoglobin ≥ 9 g/dL
- 2.1.1.1.5** Measurable disease as per the RECIST Criteria v 1.1 (see section [6.3](#))
- 2.1.1.2** For participants who will NOT receive nab-paclitaxel (Arm B1 Single Agent Lead-in only)
 - 2.1.1.2.1** Histologically confirmed solid tumor malignancy for which no curative therapy exists with at least 25% of tumor cells expressing mesothelin as determined by NCI Laboratory of Pathology. Determination can be made using archival tumor tissue or fresh biopsy. Subjects with epithelioid mesothelioma and pancreatic adenocarcinoma are automatically eligible and are not required to have this test
 - 2.1.1.2.2** ECOG performance status (PS) 0–2 ([Appendix A](#)).
 - 2.1.1.2.3** Adequate hematological function: neutrophil count of $\geq 1.0 \times 10^9$ cells/L, platelet count of $\geq 85,000/\mu\text{L}$, hemoglobin ≥ 8.5 g/dL
 - 2.1.1.2.4** Measurable and/or evaluable disease as per the RECIST Criteria v 1.1 (see section [6.3](#))
- 2.1.1.3** For all arms of the protocol
 - 2.1.1.3.1** Participants must have received at least one prior chemotherapy regimen for their disease.
 - 2.1.1.3.2** Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of LMB-100 alone or in combination with *nab*-paclitaxel in persons <18 years of age, children are excluded from this study.
 - 2.1.1.3.3** Participants must be more than 14 days removed from most recent minor surgical procedure (such as biliary stenting), 28 days from most recent major surgical procedure, 14 days removed from most recent radiation therapy, chemotherapy or experimental drug treatment with published half-life known to be 72 hours or less and 28 days removed from last experimental drug treatment with unpublished or half-life greater than 72 hours.
 - 2.1.1.3.4** All acute toxic effects of any prior radiotherapy, chemotherapy, experimental drug treatment or surgical procedure must have resolved to Grade ≤ 1 , except alopecia (any grade) and peripheral neuropathy.
 - 2.1.1.3.5** Serum albumin ≥ 2.5 mg/dL without intravenous supplementation
 - 2.1.1.3.6** Adequate liver function: Bilirubin, AST and ALT $< 2.5 \times$ ULN. AST and ALT up to $5 \times$ ULN is permitted for patients with liver metastases.
 - 2.1.1.3.7** Adequate renal function: creatinine clearance (by Cockcroft Gault formula [Appendix B](#) or measured) ≥ 50 mL/min.
 - 2.1.1.3.8** Must have left ventricular ejection fraction $\geq 50\%$
 - 2.1.1.3.9** Must have an ambulatory oxygen saturation of $> 88\%$ on room air
 - 2.1.1.3.10** The effects of LMB-100 alone or in combination with nab-paclitaxel on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry until 3 months the last dose of study therapy. 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.

2.1.1.3.11 Ability of participant to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Exclusion criteria for all study arms

2.1.2.1.1 Known or clinically suspected CNS primary tumors or metastases including leptomeningeal metastases. History or clinical evidence of CNS metastases unless they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days.

2.1.2.1.2 Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant pulmonary disease other than that related to the primary cancer, uncontrolled diabetes mellitus, and/or significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, unstable angina, or clinically significant pericardial effusion)

2.1.2.1.3 Any known diagnoses, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition (other than mesothelin [+] cancer diagnosis) that would contraindicate the use of an investigational drug, interfere with tumor measurement or lead to an expected life expectancy of less than 6 months as judged by the investigator

2.1.2.1.4 Active or uncontrolled infections.

2.1.2.1.5 Live attenuated vaccinations within 14 days prior to treatment

2.1.2.1.6 Dementia or altered mental status that would prohibit informed consent

2.1.2.1.7 Pregnant women are excluded from this study because the effects of LMB-100 on the developing fetus are unknown and may have the potential to cause 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, breastfeeding should be discontinued if the mother is treated with LMB-100. These potential risks may also apply to other agents used in this study.

2.1.2.1.8 Known hypersensitivity to any of the components of LMB-100

2.1.2.1.9 Baseline QTcF interval of > 470 ms, participants with baseline resting bradycardia < 45 beats per minute, or baseline resting tachycardia > 100 beats per minute.

2.1.2.2 Exclusion criteria specific to patients who will be receiving nab-paclitaxel (all arms except Arm B1 Single Agent Lead-in)

2.1.2.2.1 Participants with contra-indication and/or history of severe hypersensitivity reactions to *nab-paclitaxel*

2.1.2.2.2 Participants with baseline peripheral neuropathy greater than grade 2.

2.1.2.2.3 HIV or active HBV or HCV infection due to risk of progression while receiving immunosuppressive chemotherapy

2.2 SCREENING EVALUATION

Assessments will be performed any time prior to study enrollment.

- Archival tumor sample for NCI LP confirmation of diagnosis. A block of primary tissue (or 10 unstained sections on charged slides) from the time of diagnosis will be required from each participant. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable. Referring institutions will send the tumor block or 10 unstained sections on charged slides to CCR/NCI for correlative studies and confirmation of diagnosis. A fresh biopsy may be collected if tumor tissue is not available.
- For patients on the Arm B1 Single Agent Lead-in who do not have a diagnosis of epithelioid mesothelioma or pancreatic adenocarcinoma ONLY: archival tissue or fresh biopsy samples sufficient to assess tumor MSLN expression by immunohistochemistry analysis.

Assessments performed within 28 days prior to study enrollment

- History and physical exam
- Vital signs including ambulatory oxygen saturation by pulse oximetry
- ECOG performance status
- Pregnancy test in women of childbearing potential
- 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
- 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, CK, vitamin D, 1,25-dihydroxy, Coagulation (PT, PTT), lactate dehydrogenase
- CA 19-9 serum tumor marker for pancreatic cancer patients (or other appropriate tumor marker for patients enrolled in Arm B1 Single Agent Lead-in who do not have pancreatic cancer)
- Testing for HIV, HCV, HBV: anti-HIV antibody, Anti-HCV Antibody, HBs Ag Screening (except for Arm B1 Single Agent Lead-in)
- Urinalysis

2.3 REGISTRATION PROCEDURES

2.3.1 Arm B1, Single Agent Lead in Cohort Subjects with Diseases other than Epithelioid Mesothelioma or Pancreatic Adenocarcinoma Only

Registration will be a two-part process as patients in this cohort that are not diagnosed with pancreatic adenocarcinoma or epithelioid mesothelioma are screened on this protocol. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. To initially register a subject after the participant has signed the consent, complete the top portion the registration Eligibility Checklist from the website (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) indicating that the patient is being registered for screening and send via encrypted email to: NCI Central Registration Office

ncicentralregistration-1@mail.nih.gov. Once eligibility is confirmed after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and email the completed registration checklist to the CRO at NCI Central Registration Office ncicentralregistration-1@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section [3.5.2.1](#).

2.3.2 All other subjects

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-1@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the participant on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.3 Treatment Assignment Procedures

Cohorts

Number	Name	Description
A1	Phase I Short Infusion Cohort	The first 6 – 12 subjects with pancreatic cancer meeting nab-paclitaxel eligibility criteria* to determine an MTD for part A.
A2	Phase II Short Infusion Cohort	The next 14 – 20 subjects with pancreatic cancer meeting nab-paclitaxel eligibility criteria* (until at least 13 subjects have been evaluated at the Part A MTD [stage 1]– a determination will then be made on whether to continue to 20 [stage 2])
B1	Continuous Infusion, Single Agent Lead-In Cohort	Up to 30 evaluable subjects with pancreatic cancer not meeting nab-paclitaxel eligibility criteria* or subjects with other mesothelin expressing tumors for part B MTD determination.
B2	Continuous Infusion, Combination Therapy Cohort	Up to 6 subjects with pancreatic cancer meeting nab-paclitaxel eligibility criteria, followed by an additional 4 subjects if safety is established.

* criteria specific for nab-paclitaxel are found in sections [2.1.1.1](#) and [2.1.2.2](#); criteria specific for subjects not receiving nab-paclitaxel are found in section [2.1.1.2](#)

Arms

Number	Name	Description
A1	Phase I, Short infusion	Subjects infused with escalating doses of LMB-100 on days 1, 3 and 5 of each 21-day cycle. Infusion length 30 – 180 minutes. Subjects will also receive nab-paclitaxel on day 1 of each cycle.
A2	Phase II, Short infusion	Subjects infused at the LMB-100 dose determined in A1. Subjects will also receive nab-paclitaxel on day 1 of each cycle.
B1	Continuous Infusion, Single Agent Lead-In	Subjects infused with LMB-100 monotherapy at escalating doses or escalating durations once per cycle– duration may range from 24 – 96 hours
B2	Continuous Infusion, Combination Therapy	Subjects infused with LMB-100 at the dose level/dose duration determined after B1 is complete. Subjects will also receive nab-paclitaxel on day 1 of each 14-day cycle.

Arm Assignment

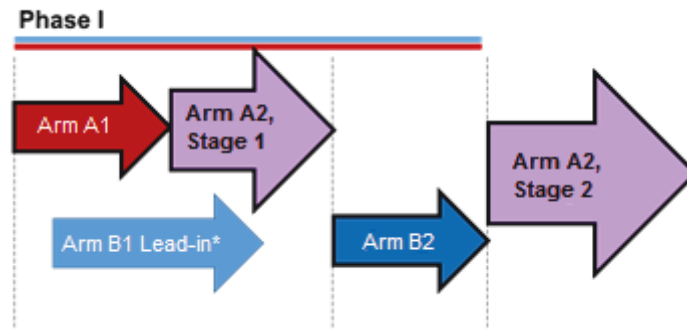
Subjects will be directly assigned to each arm as follows:

- Subjects in Cohort A1 will be directly assigned to Arm A1.
- Subjects in Cohort A2 will be directly assigned to Arm A2 once an MTD has been determined in Arm A1. Accrual to stage 2 of Arm A2 may commence after stage 1 is completed, but priority will be given to Arms B1 and B2. Note: Cohort/Arm A2 will not be opened if dose level -1 is not deemed safe in part Cohort/Arm A1.
- Subjects in Cohort B1 will be enrolled concurrently with subjects in Arm A1 & Arm A2 (if this arm is opened) and will be directly assigned to Arm B1. Priority will be given to Arm A1 followed by B1 then A2.
- Subjects in Cohort B2 will be enrolled after Cohort/Arm B1. These subjects are directly assigned to Arm B2. Enrollment to Arm B2 will be given priority over Arm A2 if these arms enroll concurrently.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

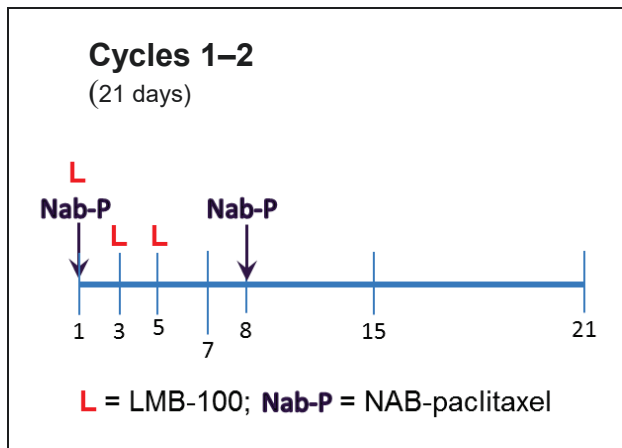
This is a first-in-human, open-label, Phase I/II study of LMB-100. It will be conducted in four parts. Three of the four parts accrue the same population of patients with advanced pancreatic cancer (indicated by black outline around the arrows in the schema below):



- Arm A1 (Phase I study): Dose escalation of short infusion LMB-100 with fixed dose nab-paclitaxel in patients with advanced pancreatic cancer
- Arm B1 Single Agent Lead-in: Dose escalation of continuous infusion LMB-100 as a single agent in patients with any solid tumor malignancy expressing MSLN. This part will run concurrently with Arm A1 since it accrues a different patient population.
- Arm B2: Single dose level of continuous infusion LMB-100 with fixed dose nab-paclitaxel in patients with advanced pancreatic cancer. This part can begin accrual after completion of Arm B1 Single Agent Lead-in.
- Arm A2 (Phase II study): Investigates the clinical activity at MTD and/or RP2D for short infusion combination therapy with *nab*-paclitaxel in a 2-stage design. The arm may not be explored if dose level -1 is deemed to be unsafe in Arm A1. If Arm A2 is opened, stage 2 will only be accrued if pre-specified response criteria for Stage 1 are met. Priority will be given to accrual of Arm B2 (which requires the same patient population) over either stage of Arm 2.

* Eligibility requirements allow for accrual of patients with any solid tumor malignancy that expresses MSLN. Participants in this arm will NOT receive nab-paclitaxel

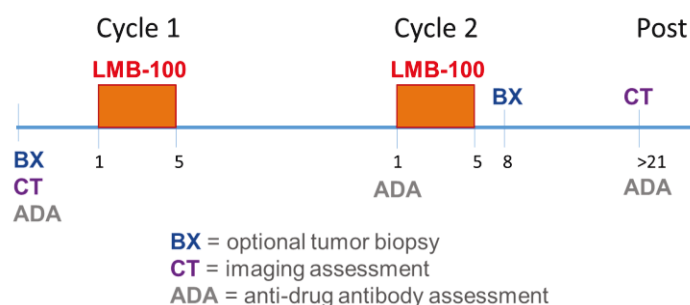
3.1.1 Study Schema for short infusion LMB-100 with nab-paclitaxel (Arm A1 (Phase I))



Participants will be treated with short infusion LMB-100 in combination with *nab*-paclitaxel for 2 cycles or until unacceptable toxicities, disease progression (per PI discretion), withdrawal from treatment for other reasons, or death, whichever occurs first. During the phase I portion of the study, participants who withdraw prior to completing the DLT assessment period (for any reason other than toxicity) will be replaced.

Arm A1 (Phase I) will utilize a dose escalation with LMB-100 administered in combination with a fixed dose of *nab*-paclitaxel (IV, 125 mg/m²). All cycles will be 21-days. *Nab*-paclitaxel will be administered on days 1 and 8. Participants will receive LMB-100 IV over 30 -180 minutes on Days 1, 3 and 5 (QOD x3).

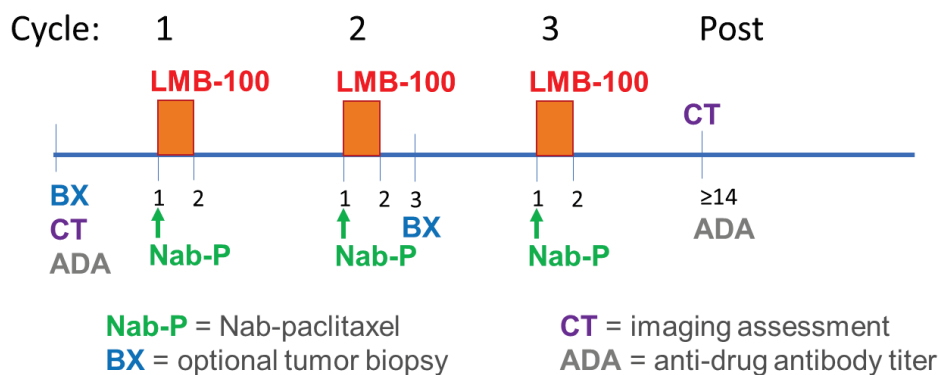
3.1.2 Study Schema for continuous infusion LMB-100 (Arm B1 [Single Agent Lead-in])



Participants will be treated with LMB-100 by continuous infusion over 24 - 96 hours with or without a loading dose depending on dose level for 2 cycles or until unacceptable toxicities, disease progression (per PI discretion), withdrawal from treatment for other reasons, or death, whichever occurs first. During the phase I portion of the study, participants who withdraw prior to completing the DLT assessment period, for any reason other than toxicity, will be replaced.

This arm will utilize a dose escalation of LMB-100. All cycles will be 21-days. Participants will receive continuous infusion of LMB-100 IV for the 1, 2, 3 or 4 days of each cycle depending on dose level.

3.1.3 Study Schema for continuous infusion LMB-100 with *nab*-paclitaxel (Arm B2)



Up to 6 evaluable participants will be treated with LMB-100 by continuous infusion over 24 hours with a loading dose in combination with nab-paclitaxel for 3 cycles of 14 days duration or until unacceptable toxicities, disease progression (per PI discretion), withdrawal from treatment for other reasons, or death, whichever occurs first. The DLT period will include the first 28 days following initial infusion of LMB-100 on C1D1. Participants who withdraw prior to completing the DLT assessment period, for any reason other than toxicity, will be replaced. Participants may be enrolled concurrently. If no more than 2 of the 6 evaluable subjects experience unacceptable toxicity (as defined by DLT criteria in section [3.1.5](#)), up to 4 additional participants may be accrued concurrently to better assess the safety and activity of this regimen.

This arm will utilize a single dose of LMB-100 in combination with a fixed dose of *nab*-paclitaxel (IV, 125 mg/m²). All cycles will be 14 days. Nab-paclitaxel will be administered on Day 1. Participants will receive a 24-hour infusion of LMB-100 IV on Day 1 of each cycle for a total of 3 cycles.

3.1.4 Study Schema for Phase II

Participants enrolled on the Phase II portion of the trial will be treated using the same schedule of short infusion LMB-100 and nab-paclitaxel as given for Arm A1 (See Section [3.1.1](#)), at the 65 mcg/kg dose of LMB-100, the RP2D in Part A. They will be treated for 2 cycles or until unacceptable toxicities, disease progression (per PI discretion), withdrawal from treatment for other reasons, or death, whichever occurs first. During the phase II portion of the study, participants who are not evaluable for response assessment will be replaced.

The phase II study (Arm A2) will be conducted in a Simon Minimax two stage phase II design. The first stage will enroll 13 evaluable participants, including the six participants treated at 65 mcg/kg. If 1 or more has a response, then accrual would continue until a total of 20 evaluable participants have been enrolled.

3.1.5 Dose Limiting Toxicity

The DLT period for Arm A1, A2 and B1 will consist of the 21 days following first administration of LMB-100 (1 cycle), while that for Arm B2 will include 28 days following first administration of LMB-100 (2 cycles). For the purpose of this study, a DLT will be defined as any of the following events attributed to LMB-100 (i.e. related to LMB-100) and occurring during the DLT period:

Hematological toxicities:

- Grade 4 neutropenia (i.e. absolute neutrophil count (ANC) $<0.5 \times 10^9$ cells/L) for a minimum duration of 7 days)
- Grade 3 and 4 febrile neutropenia (i.e. ANC $< 1.0 \times 10^9$ cells/L with a single temperature of $>38.3^\circ\text{C}$ or a sustained temperature of $\geq 38^\circ\text{C}$ for more than one hour)
- Grade 4 thrombocytopenia ($\leq 25.0 \times 10^9$ cells/L)
- Grade 3 thrombocytopenia associated with bleeding episodes

Grade ≥ 3 non-hematological toxicity with the exception of:

- Grade 3 nausea and vomiting without appropriate treatment
- Grade 3 diarrhea lasting for ≤ 2 days with no fever or dehydration
- Grade 3 infusion-related reactions are not considered to be DLTs since, based on

experience with monoclonal antibodies, IRRs are idiosyncratic and not dose-related events.

- Asymptomatic grade 3 elevation of ALT, AST, GGT, bilirubin or alkaline phosphatase attributable to study drug that persists for less than 7 days. (Please note that all grade 4 elevations in these parameters should be considered a DLT)
- Asymptomatic laboratory values (other than ALT, AST, GGT, bilirubin, alkaline phosphatase or creatinine) of Grade 3 that are judged not clinically significant by the investigator.
- **Isolated** Grade 3 fever (**without signs and/or symptoms of an infection**) occurring within 48 hours of LMB-100 infusion and resolving within 48 hours to \leq Grade 2 and fully resolved within 1 week

Grade \geq 4 non-hematological toxicity:

- Infusion-related reactions

Other toxicities:

- Any other drug related toxicity considered significant enough to be qualified as a DLT in the opinion of the principal investigator.

If a participant experiences a DLT of any grade, the investigator will have the option to either stop the LMB-100 treatment or to resume the treatment at the next lowest dose level of LMB-100 based on best clinical judgment. This can be done to allow participants, who could potentially benefit from LMB-100, to remain on the study drug treatment, if considered the most beneficial therapeutic option for the participant while managing and monitoring the participant's safety risks.

3.1.6 Dose Escalation

Dose escalation will proceed in cohorts of 3–6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during cycle 1, and the dose below that at which at least 2 (of ≤ 6) participants have DLT from the study drug. If a participant did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level to ensure that at least 3 participants in each cohort have been assessed for the full DLT period prior to moving to the next dose level. If 2 or more DLTs occur at dose level 1, dose level -1 will be evaluated.

3.1.6.1 Dose escalation tables.

3.1.6.1.1 Arm A1 (Phase 1 short infusion)

Dose Escalation Schedule Arm A1 (Phase I)	
Dose Level	Dose of LMB-100 in $\mu\text{g}/\text{kg}$
Level -1	65
Level 1	100
Level 2	140

3.1.6.1.2 Arm B1 (Single Agent Lead-in Continuous Infusion)

Table 9

Dose/ Duration Escalation Scheme		
	LMB-100 (mcg/kg/day)	Schedule
Level 1	65	48h
Level 2	100	48h
Level 3	100	24h, D1 & 4
Level 3R	100	24 h, D1 only
Level 4	140	24 h, D1 &4
R(educed) - As the occurrence of more than 1 DLT will not automatically trigger a return to a previously attempted dose level, dose levels with an R designation will be identified for exploration as the study proceeds should more than 1 DLT occur in a previously named dose level		

Table 10

Dose Steps	LMB-100 (mcg/kg/day)
I	65
II	100
III	140
IV	200

Table 11

Duration Steps	Infusion Duration (hrs)
A	24
B	24, D1 & D4
C	48
D	72
E	96

For Arm B1 (Single Agent Lead-in), the initial dose for Level 1 was defined at 65 mcg/kg/day over 48 hours and was completed after accrual of 3 participants (2 of whom were evaluable for

DLT). No safety or efficacy signal was observed at this dose level. Based on these results, Dose Step I (65 mcg/kg/d) may no longer be used, such that the minimum Dose Step after Dose Level 1 is Dose Step II (100 mcg/kg/d). Beginning with Level 2, participants will receive short infusion of 40 mcg/kg LMB-100 over the first 30-180 minutes followed by the continuous infusion defined in [Table 9](#). DLT was observed in 1/6 patients at Level 2, and testing proceeded to Level 3, a planned dose de-escalation. After accruing 6 patients to dose level 3, 3 of which were evaluable for toxicity due to hold of day 4 dose for toxicity unrelated to study drug, it was determined by the investigator to close this arm of the and begin accrual to Arm B2.

If a Level is determined to be unsafe as defined in section [3.1.6.1.3](#), then: a) the preceding Level may be declared the MTD, or b) additional Levels may be tested so long as either the dose or the duration of infusion is stepped down) to a lower level that has not been previously tested as pre-defined in [Table 10](#) and [Table 11](#). Such doses carry the R designation for reduced in [Table 9](#). For this arm of the study, there is no pre-defined number of dose levels. Dose tuning may continue until both the maximum drug dose and duration of infusion are defined or a maximum of 30 participants are treated on this arm. As dose tuning progresses, slots must be reserved in a manner that insures at least 6 participants can be treated at the RP2D.

For Arm B2, a single dose of LMB-100 has been chosen based upon safety and tolerability seen with single agent LMB-100 given in continuous infusion format in Arm B1 and taking into consideration safety and tolerability seen in Arm A1 with the combination. Given the low incidence of VLS causing weight gain greater than 5 kg with 24-hour continuous infusion given on Day 1 and that 48-hour continuous infusion given on Day 1 is the MTD for long infusion, the following LMB-100 dose will be tested in combination with standard nab-paclitaxel (125 mg/m²):

- 40 mcg/kg IV loading dose of LMB-100 given over 30 minutes (to follow nab-paclitaxel administration by 30 minutes ±20 minutes) on Day 1
- 100 mcg/kg LMB-100 IV given over 24 hours to immediately following loading dose

These drugs will be given on a 14-day cycle to improve tolerability, rather than giving nab-paclitaxel on Days 1 and 8 as in Part A.

3.1.6.1.3 Dose finding will follow the rules outlined in the Table below.

Number of Participants with DLT at a Given Dose Level	Escalation /De-Escalation Decision Rule
0 out of 3	Enter up to 3 participants at the next (integer) dose level OR may treat 1-3 additional participants to better define safety signal.
≥ 2	<p>Per the discretion of the investigator, dose escalation may be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional participants will be entered at the next lowest previously explored dose level that resulted in fewer than 2 DLTs if only 3 participants were treated previously at that dose.</p> <p style="text-align: center;">OR</p> <p>Enter up to 3 participants at the next dose level (R designation) meeting criteria of not previously explored and at either lower dose or lower infusion duration</p>
1 out of 3	<p>Enter up to 3 more participants at this dose level.</p> <ul style="list-style-type: none"> • If 0 of these 3 participants experience DLT, proceed to the next integer dose level. • If 1 or more of this group suffer DLT, then: <ul style="list-style-type: none"> ○ dose escalation may be stopped per PI discretion, and this dose is declared the maximally administered dose. UP to three (3) additional participants will be entered at the next lowest dose level that resulted in fewer than 2 DLTs if only 3 participants were treated previously at that dose. <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> ○ Enter up to 3 participants at the next dose level (R designation) meeting criteria of not previously explored and at either lower dose or lower duration
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is the MTD.

3.2 DRUG ADMINISTRATION

Standard templates for a Chemotherapy Note for a patient on this study are available in [Appendix C](#).

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 or group allocation of each participant.

Short infusion LMB-100 will be given as an IV solution on Days 1, 3 and 5 (QOD x3) of a 21-day cycle. Infusion duration should be 30-180 minutes. Continuous infusion LMB-100 will be given as an IV solution by syringe driver pump 1, 2, 3 or 4 days of a 21-day cycle depending on dose level. For continuous infusion Levels 2 and above, a loading dose of 40 mcg/kg LMB-100 given as an IV solution over 30-180 minutes will precede the start of continuous infusion on Day 1 and if applicable, Day 4.

LMB-100 must be administered in a hospital or clinic equipped for IV chemotherapy. Full emergency resuscitation facilities should be immediately available and participants 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 General Instructions

1. LMB-100 drug product should be inspected visually for particulates prior to administration.
2. LMB-100 is to be handled following all hazardous precautions.
3. Do not use the solution if there is particulate matter or if it is discolored.
4. Do not shake or freeze the vial contents.
5. Ensure the drug vial content is protected from light during preparation and administration (ambient light conditions are acceptable but avoid exposure to direct sunlight).
6. LMB-100 drug product does not contain any preservatives. Vials are for single use only and partially used vials must not be reused.
7. Any unused product should be kept for drug reconciliation.
8. No dilution of LMB-100 drug product into 0.9% saline bags should be performed.
9. Do not administer as IV push or bolus.
10. 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.

3.2.1.2 Specific Instructions

LMB-100 is diluted with 0.9% NaCl **in-line** immediately prior to administration (see [Figure 8](#) below).

The undiluted LMB-100 drug product (DP), filled in a disposable syringe, is administered by intravenous syringe infusion using a syringe driver pump. So as not to compromise drug product physico-chemical stability, the dilution with 0.9% NaCl should be done **in line**, immediately prior to administration of the neat DP.

In order to allow **in-line dilution (1:10) immediately prior** to administration of neat drug product, a side flow with 0.9% NaCl must be applied (as illustrated in [Figure 8](#)). The side flow should be set-up at 1:10 in order to deliver 0.1 mg/mL DP. During continuous infusion, the minimum rate for 0.9% NaCl infusion should be 20 mL/ hour (to prevent line occlusion), even if this results in a less concentrated infusion of study drug. An IV infusion pump and syringe driver should be used to control the infusion rate of isotonic 0.9% NaCl solution and LMB-100 respectively.

LMB-100 must be administered using a central venous catheter or an existing mediport for infusions lasting longer than 150 minutes. Central line access is neither required nor anticipated for patients in the short-infusion cohorts; however, a central line or use of an existing mediport may be permitted per PI discretion. For continuous infusion, syringes should be switched out every 12 hours (± 1 hour), which will require 2 syringes per 24 hour infusion, 4 syringes per 48 hour infusion, 6 syringes per 72 hour infusion and 8 syringes per 96 hour infusion.

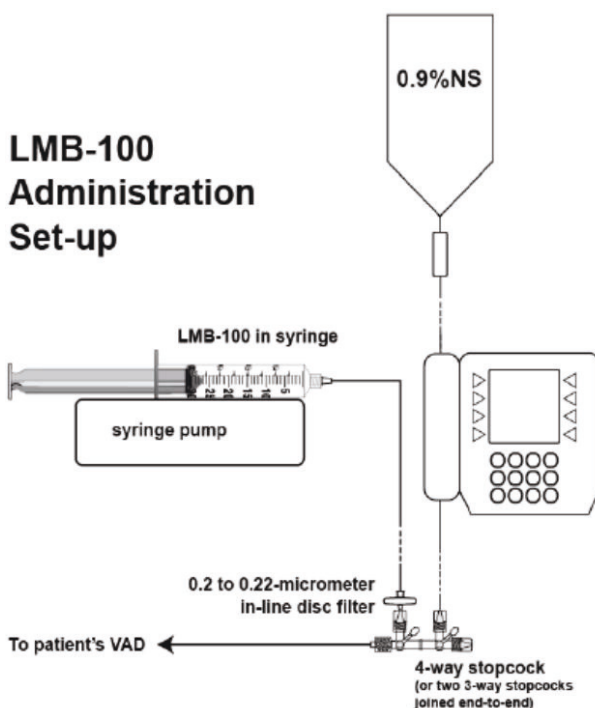


Figure 8: Schematic view of the administration set-up.

The stopcock will be changed every 24 hours to prevent microbial ingress. In line filters for the LMB-100 drug product as well as the saline will be used as depicted.

1. The syringes for administration must be prepared under appropriate aseptic conditions as LMB-100 drug product does not contain antimicrobial preservatives. All preparation

should be conducted under laminar flow hood with safety glasses, lab coat and arm protection and a work procedure to minimize particle contamination.

2. An in-line filter will be used to filter the undiluted drug product (LMB-100) during syringe infusion before side-flow dilution. For this, an in-line filter (0.2 or 0.22 μm pore size) should be positioned between the syringe extension line and the injection/infusion valve (see [Figure 8](#)). The filtration must occur **before** in-line dilution with 0.9% saline.

An in-line filter will be used during saline infusion as shown in [Figure 8](#).

3. Withdraw up to 3 ml excess volume of LMB-100 to the intended dosing volume into the syringe for priming and purging the syringe extension lines before administration (see step 9).
4. The prepared syringe should be stored and transported with a closing cone/stopper.
5. Since LMB-100 drug product does not contain antimicrobial preservatives and to comply with the chemical and physical in-use stability, the prepared syringes for infusion should be used immediately. If not used immediately, total storage times of prepared syringes should not exceed 12 hours to limit microbial growth in case of potential accidental contamination. Storage conditions should generally be at 2°C to 8°C, but syringes may be held at room temperature for up to a maximum of 4 hours. The temperature during syringe preparation, storage and drug administration must not exceed 25 °C.
6. A freshly prepared syringe of drug product is required for every 12 hours of LMB-100 infusion and for the loading dose. To limit the potential for microbial growth, when preparing syringes for continuous infusion, drug vials may not be stored and reused to prepare syringes at later time points. The syringe for the loading dose and that for the initial 12 hours of continuous infusion may be prepared from the same vial. All other syringes must be prepared from a fresh vial. Saline bags must be changed at least every 24 hours.
7. Continuous infusion may be stopped for a total of up to 90 minutes within each 24 hour period for logistical purposes. All stoppages should be documented in CRIS (both actual or estimated stop time and actual restart time)
8. Establish the saline flow first by flushing the lines including the 4-way stopcock and extension lines with saline.
9. Put the filled syringe in the pre-programmed syringe driver, remove the cap and attach the infusion set. Follow the syringe driver manual/local instructions regarding how to set up and prime/purge the system before the line is attached to the closed 4-way stopcock before starting the administration.
10. The end of infusion is defined as the time point at which the syringe driver finishes administering the total volume of IMP to be infused.
11. In case of any adverse events related to the infusion, please refer to the specific recommendation described in section [3.3.1](#).
12. The line for drawing blood for PK samples should be placed in the opposite extremity from the one with the infusion line.

3.2.1.3 Monitoring

3.2.1.3.1 Short Infusion

During short 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) for 2 hours after the end of the first infusion. For subsequent infusions, if no IRR has been reported, monitoring will continue for 30 minutes after the end of the infusion. Vital signs during the infusion are not required to be captured in the eCRF unless abnormalities are observed.

3.2.1.3.2 Continuous Infusion

During continuous 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) for the first two hours of the infusion, and thereafter, every 60 minutes (± 10 minutes) for the next 4 hours of the infusion, and then every 6 hours until the infusion is completed. Vital signs should also be recorded 2 hours (± 10 minutes) after the end of infusion.

3.2.1.4 Standard Pre-medication for Participants Receiving LMB-100

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

- Diphenhydramine 25-50 mg PO or IV
- Ranitidine 150 mg PO
- Acetaminophen 650 mg PO

Dexamethasone 8 mg IV should be physically available in the infusion unit in case of severe IRR during LMB-100 administration.

3.2.1.4.1 Additional Precautions at subsequent Infusions of LMB-100 in patients with prior IRR during short infusion of LMB-100

Participants receiving short infusion having experienced an IRR of Grade 2 to 4 on a previous infusion despite standard pre-mediation should also receive:

- Dexamethasone 20 mg, PO, 6-12 hours prior to LMB-100 administration, OR
- Dexamethasone 8 mg, IV, 30 – 60 minutes (+30 minutes) prior to LMB-100 administration, OR
- equivalent dose of another corticosteroid as clinically indicated

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

Participants who experienced an IRR of Grade 3 or 4 on a previous infusion where dexamethasone or another steroid was pre-administered should not receive further LMB-100 and will be discontinued from study therapy

3.2.1.4.2 Additional Precautions for administration of LMB-100 in patients with IRR during continuous infusion of LMB-10

Participants receiving continuous LMB-100 infusion having experienced an IRR of Grade 2 to 4 earlier in the current infusion or during a previous infusion despite standard pre-mediation should receive for the remainder of the infusion and all subsequent infusions accompanied by:

- Diphenhydramine 25-50 mg PO or IV, q6 hours
- Ranitidine 150 mg PO, q12 hours
- Acetaminophen 650 mg PO, q12 hours
- Dexamethasone as described earlier in this section, q12 hours

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

Participants who experienced an IRR of Grade 3 or 4 where dexamethasone or another steroid was pre-administered within the last 12 hours should not receive further LMB-100 and will be discontinued from study therapy.

Table 12 - Premedications for LMB-100

	Dose (mg)	Route
Acetaminophen	650	PO
Diphenhydramine	25-50	PO or IV
Ranitidine	150	PO
Dexamethasone PRN	8	IV
	OR	
Dexamethasone PRN	20	PO

3.2.2 *Nab-Paclitaxel*

Nab-paclitaxel will be administered according to the package inserts at a dose of 125 mg/m², intravenously over 30 minutes ± 10 minutes on Days 1 and 8 of each 21-day cycle. Detailed information about the preparation of the infusion solution and administration of *nab*-paclitaxel including information about compatible infusion bags, administration sets, and in line filters can be found in the package insert.

3.2.3 *Co-administration of Nab-paclitaxel and LMB-100*

On days when both LMB-100 and *nab*-paclitaxel are both scheduled to be administered (Day 1 of each cycle), *nab*-paclitaxel will be administered first. LMB-100 infusion will be initiated 30 minutes ± 20 minutes after completion of the *nab*-paclitaxel.

3.3 DOSE MODIFICATIONS

Potential overlapping toxicities of LMB-100 and *nab*-paclitaxel must be considered. In this context, peripheral edema (10%) and arthralgia (11-13%) have been seen with both drugs. *Nab*-paclitaxel has been shown to cause life-threatening pneumonitis in a small percentage of patients.

Symptomatology of pneumonitis related to *nab*-paclitaxel could overlap with pleuritis, which is an identified toxicity risk with LMB-100. Study participants will be carefully monitored for adverse events associated with these organ systems.

3.3.1 LMB-100

[Table 13](#) below provides a guideline on how to manage certain toxicities which are expected with LMB-100 based on preclinical studies and previous clinical experience with LMB-100 and molecules in the same class.

Table 13 - Guidelines for Managing Specific LMB-100 Adverse Events

Event	Action to Be Taken
<p>IRR/hypersensitivity reaction during <u>short infusion</u> of LMB-100 (Arms A1 and A2)</p>	<p>If an IRR/hypersensitivity develops, the infusion of LMB-100 should be temporarily interrupted. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment or concomitant medication may include IV saline, oxygen, bronchodilators, corticosteroids, and vasopressors depending on the symptoms.</p> <p>If the short infusion is interrupted (Arms A1 or A2):</p> <ul style="list-style-type: none"> ○ 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). ○ 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. ○ In the event of IRR CTCAE Grade 3, or CTCAE Grade 4 (which may include pulmonary or cardiac events) or an anaphylactic reaction: <ul style="list-style-type: none"> ▪ The infusion must be stopped and the participant should receive aggressive treatment ▪ Participants experiencing IRR CTCAE Grade 4 or anaphylaxis must be permanently discontinued from study treatment <p>For participants receiving short infusion LMB-100 who previously experienced IRR CTCAE ≥ Grade 2, the infusion rate for subsequent LMB-100 infusion should be reduced to one-half of the previous rate and corticosteroids premedication should be given 30 minutes prior to infusion in addition to standard pre-medications:</p> <ul style="list-style-type: none"> ○ Dexamethasone (20 mg PO 6 -12hrs before infusion or 8 mg IV, 30 - 60 min [+ 30 minutes] before infusion) or equivalent dose of another corticosteroid as clinically indicated

Event	Action to Be Taken
<p>IRR/hypersensitivity reaction during <u>continuous infusion</u> of LMB-100 (Arms B1 and B2)</p>	<p>If an IRR/hypersensitivity develops, the infusion of LMB-100 should be temporarily interrupted. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment or concomitant medication may include IV saline, oxygen, bronchodilators, corticosteroids, and vasopressors depending on the symptoms.</p> <p>In the event of IRR CTCAE Grade 4 (which may include pulmonary or cardiac events) or an anaphylactic reaction:</p> <ul style="list-style-type: none"> ▪ The participant should receive aggressive treatment ▪ Participants experiencing IRR CTCAE Grade 4 or anaphylaxis must be permanently discontinued from study treatment <p>In the event of IRR CTCAE Grade 1, 2, 3, upon resolution of symptoms,</p> <ul style="list-style-type: none"> ○ If the loading dose is interrupted, the remainder of the loading dose should be omitted and the patient should resume with the continuous infusion. ○ If the continuous infusion is interrupted: <ul style="list-style-type: none"> ▪ Patients should be retreated with the standard pre-medications if the infusion has already proceeded for 6 hours or more ▪ The infusion will resume at the same rate ▪ Patients should receive repeated dosing of the standard pre-medications and dexamethasone at the intervals specified in Section 3.2.1.4.2 <p>Participants receiving continuous infusion LMB-100 who have experienced IRR CTCAE \geq Grade 2 infusion, should receive:</p> <ul style="list-style-type: none"> ○ Standard pre-medications 30-60 minutes prior to start of infusion ○ Standard corticosteroids premedication should be given 30 minutes prior to subsequent infusion in addition to standard pre-medications: <ul style="list-style-type: none"> ▪ Dexamethasone (20 mg PO 6 -12hrs before infusion or 8 mg IV, 30 - 60 min [+ 30 minutes] before infusion) or equivalent dose of another corticosteroid as clinically indicated ○ Repeated dosing of standard pre-medications and dexamethasone at the following intervals: <ul style="list-style-type: none"> ▪ Dexamethasone, q12 hours ▪ Diphenhydramine, q6 hours ▪ Acetaminophen, q12 hours

Event	Action to Be Taken
	<ul style="list-style-type: none"> ▪ Ranitidine, q12 hours
Vascular leak syndrome	<p>In the event of Grade ≥ 2 CTCAE vascular leak syndrome (medical intervention indicated):</p> <ul style="list-style-type: none"> ○ Vasopressor support (e.g., phenylephrine) if indicated to stabilize blood pressure ○ Administer colloidal solutions (e.g., albumin) if there is a clinically significant, symptomatic and persistent systolic blood pressure drop, urine output significantly declines or serum albumin falls to 2.5 mg/dL or lower ○ For pulmonary congestion provide diuretic and/or albumin treatment as appropriate ○ Progressive shortness of breath may require endotracheal intubation or drainage of a pleural effusion ○ For oliguria and /or rising serum creatinine level delay LMB-100 if Grade 3 urine output (<10 mL/hr) ○ Use dopamine if participant is unresponsive to or unable to tolerate fluids. ○ 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	<ul style="list-style-type: none"> ○ Hydrocortisone (200 mg IV) or equivalent dose of another corticosteroid as clinically indicated ○ 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 ○ In the event of pleuritis resulting in mild to severe pleuritic pain, treat with analgesics or steroids as clinically indicated ○ For participants who have previously experienced pleuritis consider administration of dexamethasone 4 mg, PO bid beginning with first LMB-100 infusion and completing 24 hours after the last LMB-100 infusion of the cycle. (If participant is already receiving corticosteroids at dose and schedule at or above this amount as part of the pre-medication regimen, do not give additional steroids for pleuritis)
Dehydration	Encourage that participants maintain oral hydration (~1.5 L/ day)

Event	Action to Be Taken
Nausea	Ondansetron or another anti-emetic should be available as needed during Days 1-6 of each cycle
Renal toxicity	<p>In the event of Grade 1 or greater renal toxicity consider increasing oral or intravenous hydration, consider delaying LMB-100 administration by up to 48hrs.</p> <p>In the event of Grade 2 or great renal toxicity hold LMB-100 administration until recovery to Grade 1 or better. If this does not occur within 48hrs, no further LMB-100 should be given during the cycle.</p>
IRR = infusion related reaction; IV = intravenous; CTCAE = Common Terminology Criteria for Adverse Events	

3.3.2 *Nab-paclitaxel*

If *nab-paclitaxel* is withdrawn prior to completion of treatment, LMB-100 may still be continued in the absence of progressive disease.

3.3.2.1 Dose levels

Dose modifications of *nab-paclitaxel* for myelosuppression and other chemotherapy related toxicities will be made as per package insert.

3.4 STUDY CALENDARS

3.4.1 Calendar for patient receiving short infusion LMB-100 (Arms A1 and A2)

1 cycle = 21-days,

Unless otherwise indicated, screening assessments must occur within 28 days prior to enrollment. Cycle 1, day 1 assessments with the exception of imaging studies may occur up to 3 days prior to treatment initiation. Imaging studies must be completed \pm 7 days from the indicated time. If screening assessments are performed within the appropriate timeframe for Cycle 1 Day 1 assessments, they do not need to be repeated on that day.

Beyond cycle 1, performance status and standard laboratory assessments may be performed up to 1 day prior to the indicated time.

Dosing cycles after cycle 1 may be delayed for up to one week to accommodate schedule conflicts, Federal holidays and inclement weather, etc. They may be delayed for up to two weeks due to toxicity.

Procedure	Screening	Cycle 1-2				Post Therapy		
		Day 1	Day 3	Day 5	Day 8	Withdrawal visit ²	Safety Follow Up Visit ⁶	Long Term Follow Up
Nab-paclitaxel		X			X			
LMB-100		X	X	X				
History and PE	X	X				X	X	
Weight		X	X	X	X	X	X	
Height		X						
Vital signs ¹	X	X	X	X	X	X	X	
PS	X	X				X		
Labs ²	X	X	X	X	X	X	X	
1,25-dihydroxy Vit D	X					X		
Hepatitis and HIV screening panel	X							

Procedure	Screening	Cycle 1 -2				Post Therapy		
		Day 1	Day 3	Day 5	Day 8	Withdrawal visit ⁵	Safety Follow Up Visit ⁶	Long Term Follow Up
Urinalysis	X	X	X	X	X		X	
Pregnancy test ²	X	X					X	
Confirmation of Dx ⁴	X							
CT CAP and/or MRI	X					X	X ⁶	X ⁷
CA 19-9	X	X				X		
ECG	X	X				X	X	
Echocardiogram	X							
Ambulatory Oxygen Saturation	X							
Chest X-ray		X ⁸						
NIH Advance Directives Form ⁷		X ⁹						
PKs		Please refer to section 5.2.1						
Correlative Studies		Please refer to section 5.2.1						
Annual phone call to monitor survival and additional CA therapy								X
Adverse events			continuous			X	X	
Concomitant meds			continuous					

¹ During the infusions of all study, vital signs (heart rate, blood pressure, oxygen saturation) have to be monitored pre-infusion and every 15 minutes (± 5 minutes) during the infusion and then every 30 minutes (± 10 minutes) until 2 hours post-infusion.

² CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, C-reactive protein (CRP), creatine kinase (CK), PT, PTT, LDH

Procedure	Screening	Cycle 1 -2				Post Therapy		
		Day 1	Day 3	Day 5	Day 8	Withdrawal visit ⁵	Safety Follow Up Visit ⁶	Long Term Follow Up
³ Pregnancy test required in women of childbearing potential; i.e. premenopausal women and women \leq 2 years after menopause (menopause is defined as amenorrhea for $>$ 2 years). ⁴ Assessment may occur at any time prior to enrollment ⁵ For participants who complete both cycles of therapy, the withdrawal visit should be scheduled for any time between Day 20 of and 7 days following the end of Cycle 2. For participants who do not complete both cycles of therapy, the withdrawal visit should be scheduled 3-6 weeks from last treatment. Imaging studies do not need to be repeated if most recent were performed within the prior 20 days. ⁶ Safety follow up will occur 3 – 6 weeks after last dose of study therapy in patients that have progressed. The safety assessment will occur 6 weeks +/-2 weeks after the previous scan in those that have stable disease, partial response or complete response. The assessments listed refer to those that will be performed if the patient is seen in clinic. If withdrawal visit occurred within this timeframe, it can be used as the safety follow up visit. If the patient is unable to return to the clinic for the follow up visit, an adverse event assessment will be performed by telephone. ⁷ Scans, every 6 weeks, will only be performed until disease progression. Note: for patients on long term follow up, scans may be performed outside of NIH. ⁸ Chest x-ray to be done within 7 days prior to treatment on cycle 1 only. ⁹ As indicated in section 9.3, all subjects will be offered the opportunity to complete an NIH advanced 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.								

3.4.2 Calendars subjects in Arm B1 (single agent continuous infusion LMB-100)

3.4.2.1 24 HOUR INFUSION (on Day 1 OR Day 1 & 4)

1 cycle = 21 days

Unless otherwise indicated, screening assessments must occur within 28 days prior to enrollment. Cycle 1, day 1 assessments with the exception of imaging studies may occur up to 3 days prior to treatment initiation. Imaging studies must be completed \pm 7 days from the indicated time. If screening assessments are performed within the appropriate timeframe for Cycle 1 Day 1 assessments, they do not need to be repeated on that day.

Beyond cycle 1, performance status and standard laboratory assessments may be performed up to 1 day prior to the indicated time.

Dosing cycles after cycle 1 may be delayed for up to one week to accommodate schedule conflicts, Federal holidays and inclement weather, etc. They may be delayed for up to two weeks due to toxicity.

Procedure	Screening	Cycle 1 & 2						Post Therapy		
		Day 1	Day 2	Day 3	Day 4-5*	Day 6*	Day 8	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up
LMB-100		X	X		X					
History and PE	X	X						X	X	
Weight		X	X	X	X	X	X	X	X	
Height		C1 only								
Vital signs ¹	X	X	X	X	X	X	X ¹	X	X	
PS	X							X		
Labs ²	X	X	X	X	X	X	X ¹	X	X	
1,25-dihydroxy Vit D	X							X		
Urinalysis	X	X	X	X	X	X	X ¹	X	X	
Pregnancy test ³	X	X							X	
Confirmation of Dx ⁴	X									

Procedure	Screening	Cycle 1 & 2							Post Therapy			
		Day 1	Day 2	Day 3	Day 4-5*	Day 6*	Day 8	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up		
Assessment of tumor MSLN expression ⁴	X											
CT CAP and/or MRI	X							X	X ⁹		X ⁹	
CA 19-9 ⁵	X	X						X				
ECG	X	X	X					X	X			
Echocardiogram	X											
Ambulatory Oxygen Saturation	X											
Chest X-ray		X ¹⁰										
NIH Advance Directives Form ⁶		X ⁶										
PKs		Please refer to section 5.2.2.1										
Correlative Studies, including optional biopsy		Please refer to section 5.2.2.1										
Annual phone call to monitor survival and additional CA therapy												X
Adverse events		continuous							X	X		
Concomitant meds		continuous										

* For the D1&4 continuous infusion level only (and not for participants just getting 24 hr infusion on D1)

- 1 During continuous infusion, vital signs including, if possible, supine diastolic and systolic blood pressure, pulse rate, and oxygen saturation) must be monitored pre-infusion, every 30 minutes (± 5 minutes) for the first two hours of the infusion beginning with the start of loading dose, and thereafter, every 6 hours (± 60 minutes) until the infusion finishes. Vital signs during the first 2 hours of infusion are not required to be captured in the eCRF unless abnormalities are observed.
- 2 CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, C-reactive protein (CRP), Creatine Kinase (CK), CK, PT, PTT, LDH
- 3 Pregnancy test required in women of childbearing potential; i.e. premenopausal women and women ≤ 2 years after menopause (menopause is defined as amenorrhea for > 2 years
- 4 Assessment may occur at any time prior to enrollment
- 5 For patients with diagnosis pancreatic or biliary cancers (cholangiocarcinoma) only
- 6 As indicated in section 9.3, all subjects will be offered the opportunity to complete an NIH advanced 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.
- 7 For participants who complete both cycles of therapy, the withdrawal visit should be scheduled for any time between Day 20 of and 7 days following the end of Cycle 2. For participants who do not complete both cycles of therapy, the withdrawal visit should be scheduled 3-6 weeks from last treatment. Imaging studies do not need to be repeated if most recent were performed within the prior 20 days.
- 8 Safety follow up will occur 3 – 6 weeks after last dose of study therapy in patients that have progressed. The safety assessment will occur 6 weeks ± 2 weeks after the previous scan in those that have stable disease, partial response or complete response. The assessments listed refer to those that will be performed if the patient is seen in clinic. If withdrawal visit occurred within this timeframe, it can be used as the safety follow up visit. If the patient is unable to return to the clinic for the follow up visit, an adverse event assessment will be performed by telephone.
- 9 Scans, every 6 weeks, will only be performed until disease progression. Note: for patients on long term follow up, scans may be performed outside of NIH.
- 10 Chest x-ray to be done within 7 days prior to treatment on cycle 1 only

3.4.2.2 48 HOUR INFUSION

Unless otherwise indicated, screening assessments must occur within 28 days prior to enrollment. Cycle 1, day 1 assessments with the exception of imaging studies may occur up to 3 days prior to treatment initiation. Imaging studies must be completed \pm 7 days from the indicated time. If screening assessments are performed within the appropriate timeframe for Cycle 1 Day 1 assessments, they do not need to be repeated on that day.

Beyond cycle 1, performance status and standard laboratory assessments may be performed up to 1 day prior to the indicated time.

Dosing cycles after cycle 1 may be delayed for up to one week to accommodate schedule conflicts, Federal holidays and inclement weather, etc. They may be delayed for up to two weeks due to toxicity.

Procedure	Screening	Cycle 1 & 2						Post Therapy		
		Day 1	Day 2-3	Day 4	Day 5	Day 8	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up	
LMB-100		X	X							
History and PE	X	X					X	X		
Weight		X	X	X			X	X		
Height		C1 only								
Vital signs ¹	X	X	X	X			X ¹	X		
PS	X	X						X		
Labs ²	X	X	X	X			X ¹	X		
1,25-dihydroxy Vit D	X						X			
Urinalysis	X	X	X	X			X ¹	X		
Pregnancy test ³	X	X						X		
Confirmation of Dx ⁴	X									

Procedure	Screening	Cycle 1 & 2						Post Therapy			
		Day 1	Day 2-3	Day 4	Day 5	Day 8	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up		
Assessment of tumor MSLN expression ⁴	X										
CT CAP and/or MRI	X						X	X ⁹	X ⁹		
CA 19-9 ⁵	X	X					X				
ECG	X	X	Day 3 only				X	X			
Echocardiogram	X										
Ambulatory Oxygen Saturation	X										
Chest X-ray		X ¹⁰									
NIH Advance Directives Form ⁶		X ⁶									
PKs		Please refer to section 5.2.2.2									
Correlative Studies, including optional biopsy		Please refer to section 5.2.2.2									
Annual phone call to monitor survival and additional CA therapy										X	
Adverse events		continuous						X	X		

Procedure	Screening	Cycle 1 & 2				Post Therapy		
		Day 1	Day 2-3	Day 4	Day 5	Day 8	Withdrawal visit ⁷	Safety Follow Up Visit ⁸
Concomitant meds		continuous						

1 During continuous infusion, vital signs including, if possible, supine diastolic and systolic blood pressure, pulse rate, and oxygen saturation) must be monitored pre-infusion, every 30 minutes (\pm 5 minutes) for the first two hours of the infusion beginning with the start of loading dose, and thereafter, every 6 hours (\pm 60 minutes) until the infusion finishes. Vital signs during the first 2 hours of infusion are not required to be captured in the eCRF unless abnormalities are observed.

2 CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, C-reactive protein (CRP), Creatine Kinase (CK), PT, PTT, LDH

3 Pregnancy test required in women of childbearing potential; i.e. premenopausal women and women \leq 2 years after menopause (menopause is defined as amenorrhea for > 2 years

4 Assessment may occur at any time prior to enrollment

5 For patients with diagnosis pancreatic or biliary cancers (cholangiocarcinoma) only

6 As indicated in section 9.3, all subjects will be offered the opportunity to complete an NIH advanced 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.

7 For participants who complete both cycles of therapy, the withdrawal visit should be scheduled for any time between Day 20 of and 7 days following the end of Cycle 2. For participants who do not complete both cycles of therapy, the withdrawal visit should be scheduled 3-6 weeks from last treatment. Imaging studies do not need to be repeated if most recent were performed within the prior 20 days.

8 Safety follow up will occur 3 – 6 weeks after last dose of study therapy in patients that have progressed. The safety assessment will occur 6 weeks +/-2 weeks after the previous scan in those that have stable disease, partial response or complete response. The assessments listed refer to those that will be performed if the patient is seen in clinic. If withdrawal visit occurred within this timeframe, it can be used as the safety follow up visit. If the patient is unable to return to the clinic for the follow up visit, an adverse event assessment will be performed by telephone.

9 Scans, every 6 weeks, will only be performed until disease progression. Note: for patients on long term follow up, scans may be performed outside of NIH.

10 Chest x-ray to be done within 7 days prior to treatment on cycle 1 only

3.4.3 Calendar for Subjects in Arm B2 (LMB-100 24-hour continuous infusion combination therapy)

1 cycle = 14 days

Unless otherwise indicated, screening assessments must occur within 28 days prior to enrollment. Cycle 1, day 1 assessments with the exception of imaging studies may occur up to 3 days prior to treatment initiation. Imaging studies must be completed \pm 7 days from the indicated time. If screening assessments are performed within the appropriate timeframe for Cycle 1 Day 1 assessments, they do not need to be repeated on that day.

Beyond cycle 1, performance status and standard laboratory assessments may be performed up to 1 day prior to the indicated time.

Dosing cycles after cycle 1 may be delayed for up to one week to accommodate schedule conflicts, Federal holidays and inclement weather, etc. They may be delayed for up to two weeks due to toxicity.

Procedure	Screening	All cycles			Post Therapy		
		Day 1	Day 2	Day 3	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up
Nab-paclitaxel		X					
LMB-100		X	X				
History and PE	X	X			X	X	
Weight		X	X	C1 only	X	X	
Height		C1 only					
Vital signs ¹	X	X	X	C1 only	X	X	
PS	X	X			X		
Labs ²	X	X	X	C1 only	X	X	
1,25-dihydroxy Vit D	X				X		
Hepatitis and HIV screening panel	X						
Urinalysis	X	X	X	C1 only	X	X	

Procedure	Screening	All cycles			Post Therapy		
		Day 1	Day 2	Day 3	Withdrawal visit ⁷	Safety Follow Up Visit ⁸	Long Term Follow Up
Pregnancy test ³	X	X				X	
Confirmation of Dx ⁴	X						
CT CAP and/or MRI	X				X	X ⁹	X ⁹
CA 19-9 ⁵	X	X			X		
ECG	X	X	X		X	X	
Echocardiogram	X						
Ambulatory Oxygen Saturation	X						
Chest X-ray		X ¹⁰					
NIH Advance Directives Form ⁶		X ⁶					
PKs		Please refer to section 5.2.2.1					
Correlative Studies, including optional biopsy		Please refer to section 5.2.2.1					
Annual phone call to monitor survival and additional CA therapy							X
Adverse events			continuous		X	X	
Concomitant meds			continuous				

¹ During continuous infusion, vital signs including, if possible, supine diastolic and systolic blood pressure, pulse rate, and oxygen saturation) must be monitored pre-infusion, every 30 minutes (\pm 5 minutes) for the first two hours of the infusion beginning with the start of loading

dose, and thereafter, every 6 hours (± 60 minutes) until the infusion finishes. Vital signs during the first 2 hours of infusion are not required to be captured in the eCRF unless abnormalities are observed.

- 2 CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, C-reactive protein (CRP), Creatine Kinase (CK), CK, PT, PTT, LDH
- 3 Pregnancy test required in women of childbearing potential; i.e. premenopausal women and women ≤ 2 years after menopause (menopause is defined as amenorrhea for > 2 years)
- 4 Assessment may occur at any time prior to enrollment
- 5 For patients with diagnosis pancreatic or biliary cancers (cholangiocarcinoma) only
- 6 As indicated in section 9.3, all subjects will be offered the opportunity to complete an NIH advanced 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.
- 7 For participants who complete all cycles of therapy, the withdrawal visit should be scheduled for any time between Day 20 of and 7 days following the end of Cycle 2. For participants who do not complete all cycles of therapy, the withdrawal visit should be scheduled 3-6 weeks from last treatment. Imaging studies do not need to be repeated if most recent were performed within the prior 20 days.
- 8 Safety follow up will occur 3 – 6 weeks after last dose of study therapy in patients that have progressed. The safety assessment will occur 6 weeks ± 2 weeks after the previous scan in those that have stable disease, partial response or complete response. The assessments listed refer to those that will be performed if the patient is seen in clinic. If withdrawal visit occurred within this timeframe, it can be used as the safety follow up visit. If the patient is unable to return to the clinic for the follow up visit, an adverse event assessment will be performed by telephone.
- 9 Scans, every 6 weeks, will only be performed until disease progression. Note: for patients on long term follow up, scans may be performed outside of NIH.
- 10 Chest x-ray to be done within 7 days prior to treatment on cycle 1 only

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 as indicated in the [Study Calendar](#) following the last dose of study therapy.

3.5.1 Criteria for removal from protocol therapy

- Progressive disease
- Participant has completed planned number of cycles of study therapy
- Participant requests to be withdrawn from active therapy
- Pregnancy
- Unacceptable Toxicity as defined in sections [3.1.2](#) and [3.3](#)
- Investigator discretion

3.5.2 Off-Study Criteria

- Screen failure
- Participant lost to follow-up
- Participant requests to be withdrawn from study
- Death

3.5.2.1 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-1@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter (OTC) drugs, approved dietary and herbal supplements, nutritional supplements) used by a participant from the screening period until the follow-up visit. If any treatment is given within 4 weeks prior to screening this should be reported to the investigator and recorded in the eCRF.

All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

4.1.2 Prohibited Therapy

Participants 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 during the study:

- Any other investigational therapy
- Cytotoxic chemotherapy agents other than *nab*-paclitaxel
- Radiotherapy. Note: palliative 8Gy radiotherapy is allowed.
- Immunosuppressive therapy and chronically administered glucocorticoids (high dose is considered as >20 mg of dexamethasone a day [or equivalent]) for >7 consecutive days)
- Other systemic anti-neoplastic agents and targeted therapies

If any anti-neoplastic or investigational therapies listed above are needed, the participant will be considered to have evidence of progressive neoplastic disease and have experienced treatment failure with study treatment and should be withdrawn from study treatment.

Caution should be exercised when drugs that are known to be substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4 are to be co-administered with paclitaxel. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

All concomitant treatments must be documented in the eCRF.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 LMB-100 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 will be collected in 2 mL K₂EDTA 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 Ms. Yanyu Wang in Frederick for analysis.

Leidos Biomedical, Inc.
Attention: Ms. Yanyu Wang and Dr. Jon Inglefield.
Building 469, Room 200
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 Nab-Paclitaxel Pharmacokinetic Assessments

Blood samples for the determination of plasma levels of abraxane (nab-paclitaxel) will be obtained from each patient receiving nab-paclitaxel as directed in section [5.2](#).

Bioanalytical measurements will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Clinical Pharmacology Program.

This data will be used to monitor nab-paclitaxel plasma concentrations both in the absence and presence of LMB-100 to assess any drug interactions as well as correlate to pharmacodynamic endpoints, clinical response, toxicity, and pharmacogenetic analyses.

5.1.2.1 Sample Collection

See section [5.2](#) for schedule, volumes and tube types. Blood samples will be inverted 4-5x then placed on wet ice until a member of the Blood Processing Core can pick them up and process into plasma for database entry, aliquoting and storage. Paclitaxel is stable in blood on wet ice overnight, if needed.

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.

5.1.2.3 Sample storage

Samples will be stored in the CPP.

5.1.3 Pharmacogenetic Studies

Pharmacogenetic studies will be performed to analyze the genomic DNA and assess the genotype of the most relevant drug metabolizing enzymes and transporters (DMET). DNA will be analyzed on a DMET Plus (Affymatrix) genotyping platform that tests for 1,936 genetic variations in 225 drug disposition genes, including 47 CYP (phase I metabolism) genes, 13 non-CYP (phase I metabolism) genes, 78 phase II metabolizing genes (including UGTs), 63 transporters, 4 genes involved in facilitation of drug transporters, 9 genes involved in global regulation of drug metabolizing/transporting proteins, 4 drug binding proteins, and 4 drug targets.

Of specific interest to nab-paclitaxel are polymorphisms in CYP2C8, CYP3A4/5, and ABCB1, all of which are included in the DMET analysis.

Studies will be performed by the Clinical Pharmacology Program.

5.1.3.1 Sample Collection

One blood sample will be collected per patient. See section [5.2](#) for timing, volume and tube type.

5.1.3.2 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.

5.1.3.3 Sample storage

Samples will be stored in the CPP.

5.1.4 Assessment of anti-drug antibodies (ADAs)

5.1.4.1 Sample Collection

Samples will be collected before the first dose of LMB-100 administration during each cycle. (See section [5.2](#))

Draw 2mL into K₂EDTA 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.

5.1.4.2 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.

5.1.4.3 Sample Shipping

Samples will be shipped by the CPP on dry ice to Ms. Yanyu Wang in Frederick for analysis.

Leidos Biomedical, Inc.
Attention: Ms. Yanyu Wang and Dr. Jon Inglefield.
Building 469, Room 200
Miller Drive
Frederick, MD 21702
Phone: 301-846-6905/301-846-6865

5.1.4.4 Sample Storage

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

5.1.5 *Retrospective Analysis of Mesothelin Expression in tumor tissue*

IHC analysis will be performed by the Laboratory of Pathology at NCI to determine mesothelin expression within the tumor at any time after study enrollment. Leftover tissue from archival specimens or tumor biopsies obtained at screening will be used for analysis. Specimens will be used to correlate treatment with response with mesothelin expression in an exploratory analysis.

5.1.6 *Cytokines for identification of mechanism for PE-mediated capillary leak syndrome*

PE-based RITs cause dose-limiting CLS. At low doses CLS manifests as mild and transient weight gain, hypoalbuminemia, and peripheral or facial edema. At higher doses it can cause life-threatening cardiopulmonary compromise. Previous studies in rats have indicated that pathological changes indicative of CLS onset occur within just two hours of toxin administration and even when the PE fragment lacks a targeting domain.^[41] In vitro studies with cultured endothelial cells have demonstrated that super-physiologic doses of PE-based RITs cannot induce endothelial cell toxicity unless the cells express the RIT target.^[42] Together these data suggest the hypothesis that **PE-based RITs cause CLS by triggering release of vasoactive cytokines by specific immune cells rather than through direct damage to endothelial cells.** To test this hypothesis, we will collect additional serum from participants during the first hours of standard PK measurements on

Cycle 1 Day 1 of treatment (see section [5.2](#) for specific time points). Samples will be stored for later analysis.

5.1.6.1 Specimen collection

To test this hypothesis, we will collect additional serum from participants on the days and timepoints shown in sections [5.2.1](#) and [5.2.2](#) respectively for short infusion and continuous infusion cohorts.

5.1.6.2 Sample processing

Serum collected at some time points will also be used for serum MPF measurements (see Section [5.1.11](#)) and must be aliquoted appropriately to complete both assays.

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.

Cytokine levels will be retrospectively assessed.

5.1.7 Circulating endothelial cells (CEP and CEC) for identification of mechanism for PE-mediated capillary leak syndrome

Circulating endothelial progenitor cells (CEP) and mature circulating endothelial cells (CEC) will be assessed by multiparameter flow cytometry. Cells will be analyzed for forward and side scatter, and cells expressing hematopoietic markers will be excluded. Endothelial cells will be identified using co-expression of markers, such as CD31 and CD146 for CEC, and CD31 and CD133 for CEP. The cell populations will also be analyzed for viability using scatter profiles and a vital stain, such as Hoechst 33258. Percentages of stained cells will be determined and compared with appropriate negative controls. Multiparameter flow cytometric analysis will be performed with a Miltenyi Quant equipped with FlowJo software, using a minimum of 100,000 events per analysis.

5.1.7.1 Sample Collection

Draw blood into one 8-cc CPT citrate (BD) tube at (1) baseline, just prior to beginning therapy, (2) cycle 1 at 16 to 30 hours following end of last infusion as specified in sections [5.2.1](#) and [5.2.2](#), and (3) cycle 2 day 1, prior to therapy.

5.1.7.2 Sample Processing

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel-trepel@helix.nih.gov; and Sunmin Lee- lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240 760 6330 and a lab member will pick up the sample.

5.1.8 Immune subset analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8⁺ T-cells, CD4⁺Foxp3⁻ T-cells,

Tregs, Th1, Th2 and Th17+ CD4+ T-cells, monocyte subsets, MDSC subsets. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR and/or CD40.

5.1.8.1 Sample Collection

Draw blood into two 8-cc CPT citrate (BD) tubes at (1) baseline, just prior to beginning therapy, (2) cycle 1 following end of last infusion as specified in sections [5.2.1](#) and [5.2.2](#) , and (3) cycle 2 day 1, prior to therapy.

5.1.8.2 Sample Processing

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel-trepel@helix.nih.gov; Yusuke Tomita- yusuke.tomita@nih.gov and Sunmin Lee-lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240 760 6330. Please phone the lab as soon as it is drawn and a lab member will come to pick up the blood. Please keep blood at ambient temperature.

Members of the lab will enter the samples in a secure patient database, process the samples for viable cell storage, label each sample with a unique 2D barcode, and viably store the samples. They will prepare the samples for staining, stain and run the samples by multiparametric flow cytometry (MACSQuant, Miltenyi Biotec, Bergisch Gladbach, DE), and analyze the data using FlowJo (FlowJo LLC, Ashland, OR) software.

5.1.9 Peripheral blood immune gene expression

Peripheral blood immune gene expression will be evaluated by the Trepel Lab using the NanoString nCounter® platform (NanoString Technologies, Seattle, WA). Collect peripheral blood in a PAXgene Blood RNA tube (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions. After the blood is drawn, the tube should be inverted several times and placed at room temperature. RNA will be isolated using the PAXgene Blood RNA Kit according to the manufacturer's instructions. Peripheral immune gene expression will be evaluated using the PanCancer Immune Profiling codeset of 730 immune genes and 40 control genes at baseline and post-therapy by the Trepel Lab to look for correlates of clinical response with innate or adaptive immunity.

5.1.9.1 Sample Collection

Draw blood into one 2.5 ml PAXgene RNA tube at (1) baseline, just prior to beginning therapy, (2) cycle 1 following end of last infusion as specified in sections [5.2.1](#) and [5.2.2](#), and (3) cycle 2 day 1, prior to therapy.

5.1.9.2 Sample Processing

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel-trepel@helix.nih.gov; Yusuke Tomita- yusuke.tomita@nih.gov and Sunmin Lee-lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330. Please phone the lab as soon as it is drawn and a lab member will come to pick up the blood.

5.1.10 Circulating tumor cells

Peripheral blood will be collected to correlate changes in circulating tumor cells with clinical response as well as to assess immune-mediated cell death. CTCs will be assessed using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers.

5.1.10.1 Sample Collection

Draw blood into two 7.5 ml Veridex CellSave tubes at (1) baseline, just prior to beginning therapy, (2) cycle 1 following end of last infusion as specified in sections [5.2.1](#) and [5.2.2](#) and (3) cycle 2 day 1, prior to therapy.

5.1.10.2 Sample Processing

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel-trepel@helix.nih.gov; Yusuke Tomita- yusuke.tomita@nih.gov and Sunmin Lee-lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330 and a lab member will come to pick up the blood. Please keep blood at ambient temperature. Members of the lab will enter the samples in a secure patient database, and process the samples for immediate CTC assessment. They will prepare the samples for staining, stain and run the samples by multiparametric flow cytometry (MACSQuant, Miltenyi Biotec, Bergisch Gladbach, DE), and analyze the data using FlowJo (FloJo LLC, Ashland, OR) software.

5.1.11 Treatment Effect on Tumor Microenvironment

An optional biopsy may be collected in Arm B1 on day 8 of cycle 2 and in arm B2 on day 3 of cycle 2 in order to analyze any changes in the tumor microenvironment, pre and post. The C2 D8 samples will be collected in Interventional Radiology, using image guidance techniques, including CT guidance, as required. Biopsies will be obtained from primary tumor sites and/or metastatic sites (if applicable). No more than 4 cores may be obtained per site. The biopsies collected post-treatment will be compared to those collected at the time of enrollment (section [5.1.5](#)). The samples will be assessed by immunohistochemistry in the NCI Laboratory of Pathology.

5.1.12 Serum Megakaryocyte Potentiating Factor (MPF) level

MPF is a second protein product produced by the *MSLN* gene. This product is secreted by the cell and can be detected in the circulation in some patients. We hypothesize that serum MPF level may be used as a marker of tumor response in patients with *MSLN*-producing tumors like pancreatic cancer. Also, because LMB-100 halts tumor cell protein synthesis, we hypothesize that during the time of treatment serum MPF levels may also decline due to LMB-100 effect on tumor cells. To test our first hypothesis, we will collect serum from participants pre-dose for C1 and C2 as well as at the conclusion of the study. To address our second hypothesis, we will collect serum at the end of infusion (see section [5.2](#) for specific time points). Samples will be stored for later analysis in the Cao lab.

5.1.12.1 Specimen collection

To test this hypothesis, we will collect additional serum from participants in 4 mL red SST tubes at the following time-points: Cycle 1 Day 1 pre-dose, Cycle 1 at end of infusion, Cycle 2 Day 1 pre-dose, and at the time of progression or withdrawal from study.

5.1.12.2 Sample processing

Serum collected at some time points will also be used for serum cytokine analysis (see Section [5.1.6](#)). For serum MPF analysis, aliquot 100 μ L each into two cryovials with printed labels and a sample identifier and store at -80°C . Coded, linked samples will be provided to the laboratory of Liang Cao upon request of the PI.

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.

5.2 SAMPLE COLLECTION SCHEDULE

5.2.1 Sample Collection for Patients receiving short infusion LMB-100 (Arms A1 and A2)

Timed samples should be collected within +/- 15 minutes of indicated time, except for nab-paclitaxel PKs collections drawn at 5 or more hours after the end of infusion. For these, samples should be collected with + / - 60 minutes of indicated time.

Cycle	Day	LMB-100 PKs (5.1.1.1)	Nab-paclitaxel PKs (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5)
		2 mL K ₂ EDTA tube	4 mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
Screening	Screening								X ^a
1	1	Pre-dose, EOI, 1, 2, and 4 hours after EOI	pre-infusion, half way through infusion (15-min), 2-5min prior to EOI (25-28min), EOI, and 0.5, 1, 2, 5, 8, 12, 24, 48 and 72 hr post dose.	X ^b	Pre-dose	Pre-dose, EOI, 1, 2 and 4 hours after EOI	Pre-dose	Pre-dose	
	2								
	3	Pre-dose, EOF ^c							
	5					EOI			
	6								X ^d

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5)
2	1	2 mL K ₂ EDTA tube	4 mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
	3	Pre-dose, EOI ^a			Pre-dose	Pre-dose	Pre-dose	Pre-dose	
At time of Progression					X	X			
Withdrawal Visit					X	X			
Safety Follow-up Visit					X	X			

ADA =anti-drug antibody; EOI=End of infusion; PK =pharmacokinetic; CTC=circulating tumor cell; CEC=circulating endothelial cell

- Archival tissue collection or biopsy if no tissue available (mandatory).
- Collected preferably at baseline, but may be collected at any time during the study.
- Required only for patients on Arm A1. May alternatively be drawn on day 5 to avoid a weekend draw.
- May alternatively be drawn post treatment on C1D5 to avoid a weekend draw

5.2.2 Sample Collection for Patients receiving continuous infusion of LMB-100 (Arms B1 and B2)
5.2.2.1 24-hour continuous infusion

Timed samples scheduled for within 4 hours after reference point (start of infusion or end of infusion) should be collected within +/- 15 minutes of indicated time. Those collected 4 or more hours after reference point (start of infusion or end of infusion) may be collected within +/- 60 minutes of indicated time.

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
		2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
Screening	Screening								X ^b
1	1	Pre-dose, End of loading dose, 2, and 6 hours after start of continuous infusion	Pre-infusion, half way through dose (~15-min), 2-5 min prior to EOI (~25-28min), EOI, and 0.5, 1, 2, 5, 8, 12 hours post-dose	X ^c	Pre-dose	Pre-dose, 1, 2, 4 and 6 hours after start of continuous infusion	Pre-dose	Pre-dose	
	2	EOI then 2 hours after EOI	24 hr post-dose			EOI			

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
		2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ ED TA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
	3		48 hr post-dose				24 hrs after EOI ^d	24 hrs after EOI ^d	
	4		72 hr post-dose						

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
2	1	2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
	2	Pre-dose and end of loading dose			Pre-dose	Pre-dose	Pre-dose	Pre-dose	
	3 (Arm B2 only)	EOI							X ^e
3 (Arm B2 only)	1	Pre-dose and end of loading dose							
	2	EOI							X ^e
At time of Progression					X	X			
Withdrawal Visit					X	X			

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
Safety Follow-up Visit		2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
					X	X			

ADA =anti-drug antibody; EOI =End of infusion; PK =pharmacokinetic; CTC=circulating tumor cell; CEC=circulating endothelial cell

- a. Performed only in subjects receiving nab-paclitaxel (i.e., not performed in single agent lead in)
- b. Archival tissue collection or biopsy if no tissue available (mandatory).
- c. Collected preferably at baseline, but may be collected at any time during the study.
- d. May alternatively be drawn on day prior (at least 2 hours post-EOI) to avoid a weekend draw
- e. Optional

5.2.2.2 48-hour continuous infusion

Timed samples scheduled for within 4 hours after reference point (start of infusion or end of infusion) should be collected within +/- 15 minutes of indicated time. Those collected 4 or more hours after reference point (start of infusion or end of infusion) may be collected within +/- 60 minutes of indicated time.

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
1	Screening	2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
	1	Pre-dose, End of loading dose, 2, and 6 hours after start of infusion	pre-infusion, half way through loading dose (15-min), 2-5 min prior to end of loading dose (25-28min), EOI, and 0.5, 1, 2, 5, 8, 12, 24, 48 and 72 hr post dose.	X ^c	Pre-dose	Pre-dose, 1, 2, 4 and 6 hours after start of infusion	Pre-dose	Pre-dose	X ^b
	2	24 hours after start of infusion				24 hours after start of infusion			
	3	EOI then 2 hours after EOI				EOI			
4							24 hrs after EOI ^d	24 hrs after EOI ^d	
	4								

Cycle	Day	LMB-100 PKs (5.1.1)	Nab-paclitaxel PKs ^a (5.1.2)	Pharmacogenetic studies (5.1.3)	ADA (5.1.2)	PE mediated CLS (Cytokines) and serum MPF level (5.1.6, 5.1.12)	CECs, Immune Subsets, CTCs (5.1.7, 5.1.8, 5.1.10)	Immune gene expression (5.1.9)	Tumor Sample (5.1.5, 5.1.11)
2	1	2 mL K ₂ EDTA tube	4mL in 6 mL sodium heparin tube	4-6 mL in purple top tube	2 mL K ₂ EDTA tube	4 mL red SST tube	Two 7.5 mL Veridex CellSave & three 8 mL CPT citrate tubes	2.5 mL PAXgene RNA tube	NA
	2	Pre-dose, end of loading dose and 2 hours after start of infusion			Pre-dose	Pre-dose	Pre-dose	Pre-dose	
	3	24 hours after start of infusion							
	8	EOI							X ^e
At time of Progression					X	X			
Withdrawal Visit					X	X			
Safety Follow-up Visit					X	X			

ADA =anti-drug antibody; EOI=End of infusion; PK =pharmacokinetic; CTC=circulating tumor cell; CEC=circulating endothelial cell

- a. Performed only in subjects receiving nab-paclitaxel (i.e., not performed in single agent lead in)
- b. Archival tissue collection or biopsy if no tissue available (mandatory).
- c. Collected preferably at baseline, but may be collected at any time during the study.
- d. May alternatively be drawn on day prior (at least 2 hours post-EOI) to avoid a weekend draw
- e. Optional

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 IRB notification and an executed MTA.

5.3.1 Clinical Pharmacology Program

Upon arrival in the Clinical Pharmacology Program (CPP), OCD, CCR, NCI, all samples are barcoded, with data entered and stored in Patient Sample Data Management System (PSDMS), also known as *Labrador*, the system utilized by the CPP. This is a secure program, with access to the PSDMS system limited to defined CPP personnel, who are issued individual user accounts. PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS 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. There are patient demographics that can be obtained to correlate with the samples through PSDMS. For each sample, there are notes associated with 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°C or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by the researcher assigned to the protocol. All requests are monitored and tracked in PSDMS. 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 IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

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 de-identified of personal data, with access 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 termination of this protocol, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol or an exemption from IRB approval, 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), and reported as such to the IRB.

5.3.3 Laboratory of Jane Trepel

Samples will be processed immediately by the Trepel laboratory. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate. The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

5.3.4 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 participant consent or an exemption from OHSRP.

The PI will report any loss or destruction of samples to the NIH Intramural IRB as soon as he/she is made aware of such loss. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors such as a broken freezer or lack of dry ice in a shipping container, or if a participant withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples, or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

5.4 SAMPLES FOR GENETIC ANALYSIS

Pharmacogenetic studies will be performed on this protocol as described in section [5.1.3](#) and samples will be stored and secured as described in section [5.3.1](#). Because the analysis is limited to genes that play a role in drug metabolism, none of which are currently associated with disease causing genes, incidental findings will not be returned on this study.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Study data will be recorded and stored in the C3D and Labmatrix databases. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system 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. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first. Adverse events occurring more than 30 days after the last dose of study therapy are only 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, the IRB will be notified.

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
- 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. Insert name or names: 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

The SNP arrays utilized on this study (DMET chip) cover approximately 2000 genes, which are not defined as large scale genomic data under the GDS policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants should be re-evaluated following cycle 2, then every 6 weeks (+/- 2 weeks) until disease progression. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response.

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, using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).^[43] 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 patients with pleural mesothelioma, modified RECIST criteria will be used to assess response.

ORR, DCR and PFS measured according to these criteria will be reported as exploratory objectives.

6.3.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with LMB-100.

The dose determining population will consist of all participants evaluable for DLT. Participants are evaluable for DLT if they are evaluable for toxicity and discontinued earlier due to DLT or completed the DLT observation period the first cycle during phase I and have undergone safety evaluations.

Evaluable for pharmacokinetic analysis: All participants that are evaluable for toxicity will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented with the reason for exclusion.

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

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

6.3.2 All Diseases except pleural mesothelioma

6.3.2.1 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: as ≥ 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 participant, these are preferred for selection as target lesions.

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

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

6.3.2.2 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.^[44-46] 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.^[47]

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.

6.3.2.3 RECIST 1.1 Criteria

6.3.2.3.1 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.

6.3.2.3.2 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 participant 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).

6.3.2.3.3 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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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

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

6.3.3 Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) lesions are difficult to measure reliably.^[48] Therefore modified criteria were defined in 2004 adjusting target lesion measurements to the specific needs of this disease.

6.3.3.1 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.

6.3.3.2 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.

6.3.4 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 or death, whichever occurs first.

6.3.6 Objective Response Rate

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

6.3.7 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of participants with stable disease, partial response or complete response

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization 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 participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the participant or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
 - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NIH INTRAMURAL IRB AND CLINICAL DIRECTOR (CD) REPORTING

7.2.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report on the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NIH Intramural IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

7.3 IND SPONSOR REPORTING CRITERIA

Starting from the initiation of study therapy and continuing through the first 30 days after the subject receives the last administration of the investigational agent/intervention, the investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a or equivalent, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For events that occur more than 30 days after the last administration of investigational agent/intervention, only report serious adverse events that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events as well as deaths due to progressive disease must be reported within one business day

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

7.3.1 Reporting Pregnancy

7.3.1.1 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. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form “Describe Event or Problem”.

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3 “Pregnancy, puerperium and perinatal conditions - Other (pregnancy)”** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months after the last dose of LMB-100 or nab-paclitaxel.

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 3 months after the last dose should, if possible, be followed up and documented.

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 participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each participant 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 Sponsor 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 study endpoints; adherence to the protocol, regulations, 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 an NCI 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. Safety Monitoring Committee (SMC)

7.4.3 Safety Monitoring Committee

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 STATISTICAL CONSIDERATIONS

8.1 PRIMARY ENDPOINTS

The primary objectives of this trial are to:

- 1) determine the MTD of LMB-100 in combination with chemotherapy (NAB-paclitaxel) in participants with advanced pancreatic cancer both as a short infusion and as a continuous infusion
- 2) determine the response rate of the combination as a short infusion

8.1.1 Part A

Arm A1 - Phase I. Part A begins with a two dose level escalation using a 3 + 3 design with LMB-100 potentially evaluated at 100, and 140 mcg/kg in combination with chemotherapy. A lower dose of 65 mcg/kg may also be evaluated. If both intended dose levels are explored and each requires up to 6 participants, then up to 12 participants may be required for the phase I portion of the trial. Note: Subjects enrolled prior to Amendment C (n=3) in which the maximum number of cycles was reduced, are included in the MTD evaluation as they have received at least 1 cycle of LMB-100.

After the enrollment of patients to the first 2 dose levels the pharmacokinetic and anti-drug antibody level (ADA) data will be analyzed before enrolling new patients. Dr. William Figg, who has expertise in pharmacokinetics, will, in conjunction with the NCI CCR leadership committee analyze the data. Since the thresholds for ADA and its influence on pharmacokinetics are unclear, pre-specified criteria for making changes to the protocol cannot be established at this time. The objective of the assessment will be to make recommendations as to whether a therapeutic threshold has been reached and what, if any adjustments should be made with regard to the eligibility criteria and/or study plan.

Arm A2 -Phase II portion of Part A. In Arm A2 we will evaluate the combination identified as being the MTD from Arm A1. As of 5/1/18, this is anticipated to be at dose level -1. If dose level -1 is not found to be same during Arm A1, we will not proceed to Arm A2.

If Arm A2 does proceed, since the participants to be treated on the phase II portion will have the same eligibility criteria as those on phase I, the 6 participants treated at 65 mcg/kg (the anticipated RP2D from Arm A1) will be the 6 initial participants treated on the first stage of the phase II cohort. Based upon results from two small trials of NAB-paclitaxel treatment beyond the first-line setting, the response rate of participants with advanced pancreatic cancer to NAB-paclitaxel is at most 5%.^[49, 50] It would be desirable if this were improved by 15-20% or more. As such, the goal would be to determine if using the combination would rule out a 5% response rate to target a rate of 25%. The trial will be conducted using a Simon Minimax two-stage phase II trial design^[51] in order to rule out an unacceptably low PR+CR rate of 5% ($p_0 = 0.05$) in favor of an improved response rate of 25% ($p_1 = 0.25$). With $\alpha = 0.10$ (probability of accepting a poor treatment = 0.10) and $\beta = 0.10$ (probability of rejecting a good treatment = 0.10). This first stage will enroll 13 evaluable participants, and if 0 of the 13 have a clinical response, then no further participants will be accrued. If 1 or more of the first 13 participants has a response, then accrual would continue until a total of 20 evaluable participants have been enrolled. As it may take up to several months to determine if a participant 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 1 to 2 participants with a response out of 20 participants, this would be an uninterestingly low response rate. If there were 3 or more of 20 (15%) 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 51%.

8.1.2 Part B:

Arm B1 -Phase I, Continuous Infusion Single Agent Lead-In. While patients who are eligible for enrollment into Part A are being treated on Part A, patients who have pancreatic cancer who do not meet eligibility criteria for nab-paclitaxel and patients with other MSLN-expressing solid tumors will be enrolled onto Part B Single Agent Lead-in. This portion of the trial has dose finding using a 3 + 3 design with LMB-100 alone as a continuous infusion, potentially evaluated at doses of 65, 100, 140 and 200 mcg/kg/day over 24, 24 *2, 48, 72 and 96 hours using a flexible escalation scheme. This will establish the single agent MTD for continuous infusion. Enrollment in this arm has been capped at a maximum of 30 participants being treated. If each dose level requires all 6 participants, then five dose levels may be examined.

After the first 3 patients were enrolled, the pharmacokinetic data were analyzed before enrolling new patients. Dr. William Figg, who has expertise in pharmacokinetics, in conjunction with the NCI CCR leadership committee analyzed the data. The objective of the assessment was to make recommendations as to whether drug levels near that projected by the simulation can be achieved (feasibility, safety) and what, if any adjustments should be made with regard to the dose escalation and/ or study plan. The first assessment completed just prior to the implementation of Amendment F. leading to the new dose escalation plan and the addition of a bolus dose submitted in Amendment F. Similar assessments will continue at the completion of each dose level.

Arm B2 – Continuous Infusion, Combination therapy: After the Part B Single Agent Lead-in is completed, assessment of continuous infusion of LMB-100 in combination with chemotherapy will be tested in the same population of pancreatic cancer patients enrolling in Part A. A single dose level of LMB-100 will be assessed in combination with chemotherapy in Phase I Part B. This will require a maximum of 6 additional evaluable patients. If safety and tolerability of this combination is established in these 6 patients, then an additional 4 patients will be enrolled (total of 10 patients) to complete a small pilot investigation of the response rate of the combination of continuous infusion LMB-100 and Nab-paclitaxel. This is being kept deliberately small to permit more rapid assessment of any evidence of efficacy. These 10 patients' clinical responses will be reported along with an appropriate confidence interval, and will be used to characterize the potential clinical efficacy of the combination. Therefore, 10 total participants with pancreatic cancer will be required to complete Phase I and pilot investigation of response rate.

At the conclusion of the trial, the response information from the phase II portion of Part A and the pilot in Part B will be used to identify parameters which may merit further exploration in a more definitive subsequent trial.

8.2 DETERMINATION OF SAMPLE SIZE

Part A: the phase I portion of the trial may require up to 12 participants, and the phase II portion, if explored, may require up to 20 evaluable participants. However, with 6 participants from phase I potentially being included in phase II, up to $12+20-6=26$ individual participants may be required.

Part B: The lead-in with single agent continuous LMB-100 may require up to 30 patients. Evaluation of the combination with nab-paclitaxel will require 10 patients if the combination is deemed safe and feasible. Therefore, up to 40 patients may be required.

Candidates for the phase 1 lead in portion of the study will be screened on the current protocol. With an anticipated screen failure rate of 50%, up to $30/0.5 = 60$ subjects may need to enroll to this portion of the study. With an additional 26 subjects required in part A (phase I and II) and 10 subjects in the combination therapy portion of Part B, the overall accrual ceiling will be set at 100 ($26+60+10 +4 = 100$ in order to allow for a small number of inevaluable participants). If 1-2 eligible pancreatic cancer patients enroll per month and 2-3 patients with other MSLN-expressing tumor types enroll on this trial, accrual would be expected to be completed in approximately 3 to 5 years if the second stage of Phase II Part A is reached.

9 HUMAN SUBJECTS PROTECTIONS

9.1 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). The rationale to include MSLN- positive tumors of epithelial cell origin is based on preclinical models demonstrating promising anti-tumor efficacy. In addition, molecular pathology data demonstrated a high prevalence of mesothelin protein in these tumors. The rationale to evaluate LMB-100 in advanced/metastatic PDA and in mesothelin expressing solid tumors is to preliminarily assess the safety of LMB-100 alone or in combination with the standard

of care (SoC) chemotherapy *nab*-paclitaxel and We will also assess the preliminary anti-tumor activity of LMB-100 in PDA.

9.2 PARTICIPATION OF CHILDREN

As this is a first in human study, there are no dosing or adverse event data are currently available on the use of LMB-100 in combination with *nab*-paclitaxel in participants <18 years of age; therefore, children are excluded from this study.

9.3 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 9.5), all subjects 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 MAS Policy 87-4 and 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.

9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

9.4.1 Risks from Study Drugs

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

The risks of the study include those associated with study agents as discussed in section 10. Additional risks may also be encountered from the use of the agents in combination as discussed below.

9.4.1.1 Potential Toxicities of Combining LMB-100 with *Nab*-paclitaxel

The most common clinically significant adverse reactions associated with the use of *nab*-paclitaxel have been neutropenia, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal disorders. In the *nab*-paclitaxel treated population, the most frequently ($\geq 40\%$ of participants) reported treatment emergent adverse events (TEAEs) were fatigue, nausea, peripheral neuropathy, alopecia, peripheral edema, diarrhea, anemia, neutropenia, and pyrexia. The most frequently reported Grade 3 or higher TEAEs in the *nab*-paclitaxel arm were neutropenia, fatigue, peripheral neuropathy, thrombocytopenia, and anemia.

9.4.2 Risks of study procedures

Study procedures such as research blood collection and ECGs are of minimal risk to the subject. Higher risk procedures performed include:

9.4.2.1 CT Guided Research Biopsy

The risks of the optional research biopsy collected in cycle 2 include pain, bleeding and infection at the biopsy site. In addition, as the biopsy may be collected under CT guidance, subjects in this study may be exposed to approximately 0.77 rem. This amount is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

9.4.2.2 Central Line Insertion

All subjects in Arms B1 and B2 are required to receive study therapy through a central line or an existing mediport. In addition, per PI discretion, some subjects in Arms A1 and A2 may also require central line insertion. The risks of this procedure include catheter contamination, pneumothorax, arrhythmia and air embolus. All care will be taken to minimize complications of central insertion during the procedure.

9.5 RISKS/BENEFITS ANALYSIS

Patients with advanced and/or metastatic cancer are in continuous need of improved therapy options. This is especially true for patients where no standard therapy exists such as the 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 even more so when LMB-100 has been combined with chemotherapy. Therefore, LMB-100 may improve clinical outcome of patients with pancreatic ductal adenocarcinoma in combination with *nab*-paclitaxel, an approved agent in advanced/metastatic PDA as well as the outcome of patients with mesothelin positive solid tumors receiving LMB-100 monotherapy. A number of clinically appropriate strategies to minimize risk to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines.

Overall, the potential benefits of LMB-100 for cancer participants, those able to consent and those who lose the capacity to do so during the course of the trial, outweigh the risks associated with the proposed entry-into-human trial with LMB-100.

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All participants will be thoroughly screened by the physician and the research nurse prior to completing the consent. During the initial consultation, the participant and family or friends, if present, will be presented with a forthright and detailed overview of the treatment option available to them at the NIH. The experimental nature of the treatment, its objectives, its theoretical advantages and disadvantages will be presented. The Informed Consent document is given to the participant and they are asked to review it, make notes and ask questions prior to agreeing to participate in this protocol. The participant is reassured that participation on this trial is entirely voluntary and that he/she can withdraw or decide against treatment at any time without adverse consequences. The physician assures the participant that if alternative therapy or no therapy at all is preferred, we will do all that we can to facilitate consultation with the appropriate referral organizations. Consent for optional biopsy 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.

The Informed Consent document may be obtained from the participant by the principal investigator, associate investigators, or the medical staff fellow under the supervision of the principal investigator.

9.6.1 Consent procedure for non-English speaking patients

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

9.6.2 Telephone consent procedure

Consent for screening and re-consent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator.

10 PHARMACEUTICAL INFORMATION

Nab-paclitaxel is approved for use as a first line agent in metastatic pancreatic cancer. It is not approved for use as a second line agent, the use in the current protocol. The investigation is not intended to support a new indication for use or any other significant changes to labeling or advertising in any of the commercial agents used on the study. The investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products.

10.1 LMB-100 (IND # 123332)

10.1.1 Source

LMB-100 was transferred to the NIH CC Pharmacy by Roche, the drug manufacturer. For this trial, the drug will be supplied by the NIH CC Pharmacy.

10.1.2 Toxicity

Information in this section is based on preclinical studies with LMB-100, and clinical studies of the cytolytic fusion protein SS1-P. Participants 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 ≤ 2 hematological toxicities or Grade ≤ 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 ≤ 2 hematological toxicities or Grade ≤ 1 non-hematological toxicities. If toxicity does not resolve to NCI CTCAE Grade ≤ 2 hematological toxicities or Grade ≤ 1 non-hematological toxicities and the participant is unable to resume treatment with LMB-100 after this time, no additional doses will be administered and the participant will be withdrawn from study treatment.

10.1.2.1 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. Participants may also develop IgE-mediated hypersensitivity reactions to LMB-100. IRRs may be indistinguishable from an anaphylactic reaction. Participants should receive full supportive care to treat IRRs or anaphylaxis according to institutional practice. If infusion-associated signs or symptoms occur, participants should be monitored until complete resolution.

In vitro data and previous clinical experience with LMB-100 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 [1.2.4.1.4](#)). 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.

10.1.2.2 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 participants after 1 cycle of therapy, in the IV bolus and continuous infusion trials respectively.^[31]

Participants 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.

10.1.2.3 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. Participants who develop symptoms of serosal inflammation should be closely monitored and receive standard treatments which may include corticosteroids.

10.1.2.4 Risk of Vascular Leak Syndrome

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

10.1.2.5 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.

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

10.1.2.6 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. Participants who develop symptoms of infusion site reactions can be administered pain relieving medication (analgesic) as required, and rotation of infusion sites is recommended.

10.1.2.7 Pregnancy

No studies assessing the reproductive and developmental toxicity of LMB-100 have been conducted to date. It is not known whether LMB-100 can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. LMB-100 should not be administered to pregnant women.

10.1.3 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.

10.1.4 Stability and Storage

Chemical and physical in-use stability for undiluted LMB-100 drug product in syringes has been demonstrated for 24 hours at 2-8 °C and 24 hours at ambient temperature.

Storage conditions should generally be at 2-8°C, but syringes may be held at room temperature for up to a maximum of 4 hours.

Roche has extensively studied the stability of LMB-100. Vials of LMB-100 can be stored at 4°C for at least 24 months without loss of activity or degradation of the drug product. At 25°C, no loss of activity is observed over a 4-week period, and 94% of potency is retained even after 3 months of exposure to this temperature ([Figure 9](#)). However, when vials of LMB-100 are exposed to temperatures of 37°C, the drug begins to lose activity within 12 hours.

10.1.5 Administration procedures

Please refer to section [3.2.1](#)

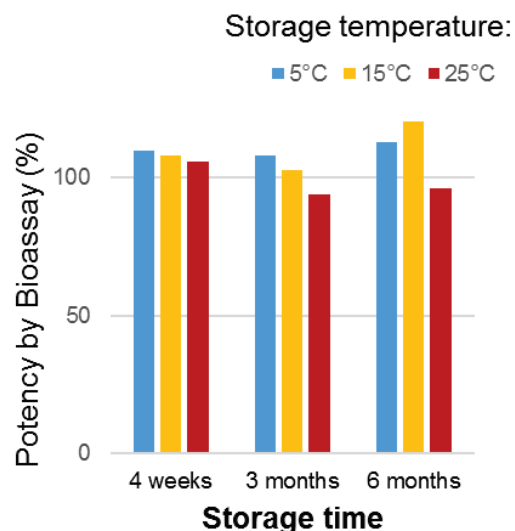
10.1.6 Incompatibilities

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.

10.1.6.1 Mechanism of action

LMB-100 is a novel recombinant anti-mesothelin targeted cytolytic fusion protein (cFP) developed for the treatment of participants 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.

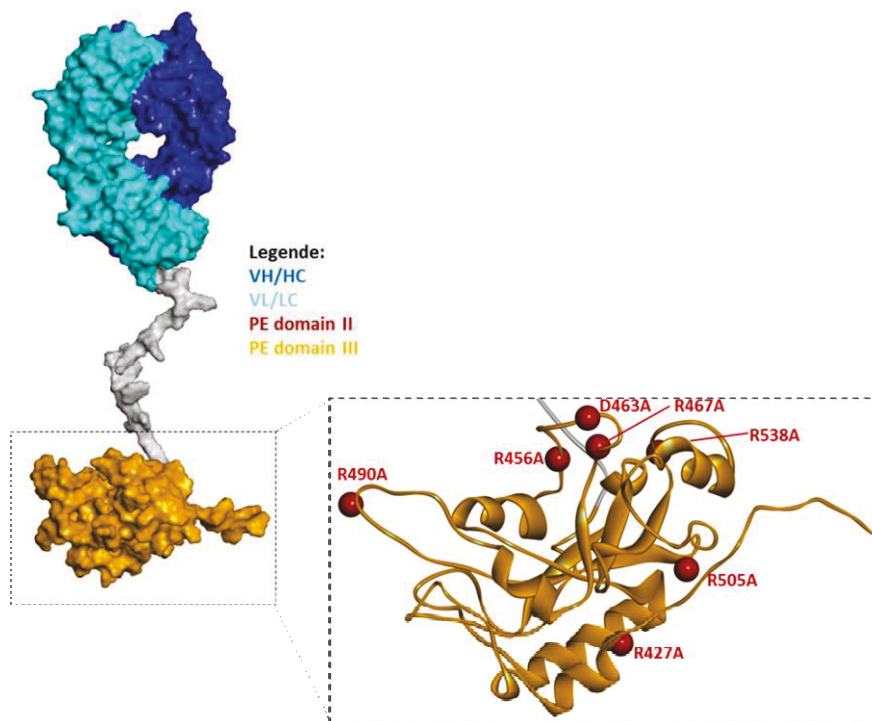
Figure 9



Adapted from Roche Stability Report, Study# 07B20140012

10.1.6.2 Molecular Weight: approximately 73 kDa

10.1.6.3 Chemical Structure



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

10.2 *NAB*-PACLITAXEL

Please refer to package insert for additional information.

10.2.1 *Source*

Nab-paclitaxel will be purchased from commercial sources by the NIH CC Pharmacy.

10.2.2 *Toxicity*

The most common clinically significant adverse reactions reported with *nab*-paclitaxel in patients with pancreatic cancer include: neutropenia, anemia, thrombocytopenia, pancytopenia peripheral neuropathy, cardiac failure, tachycardia, dyspnea, pneumonitis, nausea, vomiting, diarrhea abdominal pain, intestinal obstruction, colitisarthralgia/myalgia, renal failure, increased alanine aminotransferase, increased aspartate aminotransferase, increased bilirubin, and increased creatinine.

Hypersensitivity reactions including fatal anaphylactic reactions have rarely been reported with *nab*-paclitaxel. If a hypersensitivity reaction occurs, *nab*-paclitaxel should be discontinued immediately, symptomatic treatment should be initiated, and the participant should not be rechallenged with paclitaxel.

Bone marrow suppression (primarily neutropenia) occurs frequently with *nab*-paclitaxel. Frequent monitoring of blood cell counts should be performed. Participants should not be retreated with subsequent cycles of *nab*-paclitaxel until neutrophils recover to > 1500 cells/mm² and platelets to $> 100,000$ cells.

Sensory neuropathy occurs frequently with *nab*-paclitaxel, though generally not severe. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction.

Sepsis was reported in 5% of participants with or without neutropenia who received *nab*-paclitaxel.^[52] Complications due to underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors.

Pneumonitis occurred in 4% of participants using *nab*-paclitaxel. Closely monitor all participants for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with *nab*-paclitaxel and promptly initiate appropriate treatment with supportive measures.

Hepatic impairment may increase the toxicity of *nab*-paclitaxel, particularly myelosuppression. Administration of *nab*-paclitaxel in participants with hepatic impairment should be performed with caution.

Congestive heart failure and left ventricular dysfunction have rarely been observed in participants receiving *nab*-paclitaxel. Most of these participants were previously exposed to cardiotoxic medicinal products such as anthracyclines or had underlying cardiac history. Participants receiving *nab*-paclitaxel should be vigilantly monitored for the occurrence of cardiac events.

Nausea, vomiting, and diarrhea following administration of *nab*-paclitaxel may be treated with commonly used anti-emetics and constipating agents.

In the very elderly (≥ 75 years) who received *nab*-paclitaxel, there was a higher incidence of serious adverse reactions and adverse reactions that led to discontinuation including hematologic toxicities, peripheral neuropathy, decreased appetite, and dehydration. Participants 75 years or older should be carefully assessed for their ability to tolerate *nab*-paclitaxel with special consideration to performance status, co-morbidities, and increased risk of infections.

10.2.3 Formulation and preparation

Formulation

ABRAXANE is supplied as a lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution.

Preparation

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the participant:
Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE® into an empty, sterile IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

10.2.4 Stability and Storage

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Product should be retained in the original packaging to protect from bright light.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours...

Abbreviated Title: LMB-100 + Abrx in PDA
Version Date: 12/11/2018

10.2.5 Administration procedures

Please see section [3.2.2.](#)

10.2.6 Incompatibilities

Please refer to the package insert.

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12 APPENDICES

12.1 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.

12.2 APPENDIX B – COCKCROFT-GAULT FORMULA FOR CALCULATION OF CREATININE CLEARANCE

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft-Gault formula, which employs creatinine measurements and a patient's weight to predict the clearance. The formula, as originally published, is:

$$x = \frac{(140 - \textit{age}) \times \textit{weight}}{72 \times \textit{creatinine}}$$

This formula expects weight (actually mass) to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female. This formula is useful because the calculations are relatively simple and can often be performed without the aid of a calculator.

A modification of this formula, useful for the common units of measure, is:

$$x = \frac{(140 - \textit{age}) \times \textit{weight} \times \textit{constant}}{\textit{creatinine}}$$

This formula uses metric units (weight in kilograms, creatinine in $\mu\text{mol/L}$). The constant is 1.23 for men and 1.04 for women.

12.3 APPENDIX C: SAMPLE CHEMOTHERAPY NOTES

12.3.1 For Part A

(1)

Nab-paclitaxel, 125 mg/m², IV over 30 minutes ± 10 minutes on Days 1 and 8

(2)

LMB-100, <dose as per escalation scheme> mcg/kg, IV on Days 1, 3 and 5

On Day 1, administer 30 minutes ± 20 minutes following completion of Nab-paclitaxel infusion

Pre-medications:

- Diphenhydramine 25-50 mg PO or IV
- Ranitidine 150 mg PO
- Acetaminophen 650 mg PO

Additional medications:

-Dexamethasone 8 mg IV, PRN severe infusion related reaction (should be available on unit)

-Ondansetron 8 mg PO q8h, PRN nausea

Please encourage oral hydration of 1.5 to 2L daily while receiving LMB-100.

12.3.2 For Arm B1

(1)

Loading dose of LMB-100

LMB-100, 40 mcg/kg, IV on Day 1 and if applicable, Day 4

Continuous infusion LMB-100 to immediately following loading dose on Day 1 and if applicable, Day 4

LMB-100, <dose as per escalation scheme> mcg/kg/day IV, for # hrs

Syringes of drug must be changed q12hrs. In-line filtration required.

Dose per 12 hours = <dose as per escalation scheme> / 2 = # mcg/kg

Infusion rate = <Dose per 12 hours> / 12 = # ml/hr

Run with Normal Saline at 20cc/hour IV for in-line dilution.

Pre-medications on Day 1:

- Diphenhydramine 25-50 mg PO or IV
- Ranitidine 150 mg PO
- Acetaminophen 650 mg PO

Additional medications:

-Dexamethasone 8 mg IV, PRN severe infusion related reaction (should be available on unit)

-Ondansetron 8 mg PO q8h, PRN nausea

Please encourage oral hydration daily of 1.5 to 2L daily while receiving LMB-100.

12.3.3 For Arm B2

(1)

Nab-paclitaxel, 125 mg/m², IV over 30 minutes ± 10 minutes on Days 1

(2)

Loading dose of LMB-100

LMB-100, 40 mcg/kg, IV on Day 1

Continuous infusion LMB-100 to immediately following loading dose on Day 1

LMB-100, 100 mcg/kg/day IV, for 24 hrs

Syringes of drug must be changed q12hrs. In-line filtration required.

Dose per 12 hours = 50 mcg/kg * <patient weight> = # mg

Infusion rate = <Dose per 12 hours (mg)> / 1 mg/mL / 12 hrs = # ml/hr

Run with Normal Saline at 20cc/hour IV for in-line dilution.

On Day 1, administer 30 minutes ± 20 minutes following completion of Nab-paclitaxel infusion

Pre-medications:

- Diphenhydramine 25-50 mg PO or IV
- Ranitidine 150 mg PO
- Acetaminophen 650 mg PO

Additional medications:

-Dexamethasone 8 mg IV, PRN severe infusion related reaction (should be available on unit)

-Ondansetron 8 mg PO q8h, PRN nausea

Please encourage oral hydration of 1.5 to 2L daily while receiving LMB-100.