Abbreviated Title: LMB100 + tofacitinib in PDA

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Title: A Phase I Study of Mesothelin-Targeted Immunotoxin LMB-100 in Combination with Tofacitinib in Persons with Previously Treated Pancreatic Adenocarcinoma, Cholangiocarcinoma and other Mesothelin Expressing Solid Tumors.

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Investigational Agents:

Drug Name:	LMB-100 (formerly RO6927005)	Tofacitinib (Xeljanz)	Mesothelin Expression Testing
IND Number:	123332	123332	NSR device
Sponsor:	Center for Cancer Research (CCR), NCI, NIH	Center for Cancer Research (CCR), NCI, NIH	CCR, NCI, NIH
Manufacturer	Selecta Biosciences	Pfizer	NCI Laboratory of Pathology

Commercial Agents: none

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%.
- Cholangiocarcinoma is a rare disease and just 3,000 patients are diagnosed with the extrahepatic form yearly. The median overall survival of patients with advanced disease receiving standard of care treatment is less than 1 year.
- Expression of mesothelin (MSLN) in pancreatic ductal adenocarcinoma (PDA) has been examined in several published studies and ranges from 86 to 100%. Similar incidence of expression has been observed in extrahepatic cholangiocarcinoma.
- In addition to pancreatobiliary tumors, many other solid tumor types also express MSLN such as mesothelioma, colorectal, lung adenocarcinomas, epithelial ovarian, gastric and triple negative breast cancers, as well as some tumors of squamous cell origin.
- LMB-100 and a closely related immunotoxin also targeting MSLN have been studied in previous Phase 1 clinical studies for mesothelioma and pancreatic cancer.
- Results from these studies showed that almost all patients formed anti-drug-antibodies (ADAs) that neutralized subsequent injection of the product making it ineffective.
- Tofacitinib is an oral Janus Kinase-1 and -3 (JAK) inhibitor approved by the FDA for the treatment of rheumatoid arthritis and ulcerative colitis.
- Pre-clinical studies have shown that tofacitinib can prevent the formation of ADAs against an immunotoxin closely related to LMB-100
- Co-administration of tofacitinib with immunotoxin increased immunotoxin serum half-life in mice and enhanced anti-tumor efficacy
- This clinical trial will investigate whether co-administration of tofacitinib with LMB-100 can prevent or delay the formation of ADAs and thus allow patients to receive additional effective cycles of LMB-100.

Objectives:

- The primary objective of the dose escalation phase of this study is to assess the safety and tolerability of LMB-100 given in combination with tofacitinib to patients with pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma and other mesothelin-positive solid tumors
- The primary objective of the expansion phase of this study is to determine whether co-administration of tofacitinib delays formation of neutralizing anti-LMB-100 ADAs

through cycle 2 of treatment (as measured by LMB-100 serum drug levels) in patients with pancreatobiliary cancers.

Eligibility:

- Age ≥ 18 years
- Histologically confirmed solid tumor malignancy for which no curative therapy exists
- Participants must have received at least one prior systemic treatment regimen for their disease OR be ineligible to receive available standard treatments for their disease OR refused first-line standard systemic treatments but have been treated with other anti-cancer agents.

Design:

- This is a Phase I study which will accrue up to 45 subjects total, accounting for screen failure.
- Participants will be co-treated for 3 cycles with tofacitinib given orally for the first 10 days of each 21 day cycle, and LMB-100 given on days 4, 6 and 8.
- A 3+3 dose escalation schema will be used. Two dose levels are planned. One minus dose level could be utilized if dose de-escalation is necessary.
- Following identification of an optimal dose and schedule, an expansion phase of 15 participants will be initiated at the optimal dose for patients with pancreatic adenocarcinoma and extrahepatic cholangiocarcinoma. At least 8 participants in the expansion phase must have pancreatic adenocarcinoma.
- Participants on the Dose Escalation and Dose Expansion Arms who appear to be obtaining clinical benefit from LMB-100/tofacitinib after 3 cycles of treatment may elect to receive additional cycles of therapy at the discretion of the PI.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- For dose escalation cohort: To assess the safety and tolerability of LMB-100 with tofacitinib in patients with pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma and other mesothelin-positive solid tumors
- For dose expansion cohort: To determine whether co-administration of tofacitinib delays the formation of neutralizing anti-LMB-100 ADAs through cycle 2 of treatment (as measured by LMB-100 serum drug levels) in patients with pancreatobiliary cancers.

1.1.2 Secondary Objectives

- For the dose escalation cohort: To determine whether co-administration of tofacitinib delays formation of neutralizing anti-LMB-100 ADAs through cycle 2 of treatment (as measured by LMB-100 serum drug levels)
- For the expansion cohort: To assess the safety and tolerability of the combination in patients with pancreatobiliary cancer
- For both cohorts: To define the effect of tofacitinib on the pharmacokinetic characteristics of LMB-100
- For both cohorts: To determine the percentage of patients who have delayed formation of neutralizing anti-LMB-100 ADAs through cycle 3 of treatment (as measured by LMB-100 serum drug levels) when co-administered tofacitinib

1.1.3 Exploratory Objectives

- To obtain preliminary assessment of activity including change in appropriate serum tumor markers with treatment, objective response rate (ORR), disease control rate after 3 cycles (~9 weeks) of treatment (DCR), progression free survival (PFS) and overall survival (OS)
- Evaluate association between anti-LMB-100 antibody titer and peak serum drug level
- To examine the relationship between MSLN expression and response to treatment
- To evaluate changes in the tumor microenvironment following treatment with LMB-100 plus tofacitinib
- To assess changes in circulating immune cell and cytokine levels caused by the treatment
- For treatment extension: To determine whether tofacitinib can continue to prevent ADA formation beyond 3 cycles of treatment regardless of whether patients had another intervening therapy or not.

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.

Cholangiocarcinoma is a rare cancer type which originates in the biliary tract. Extrahepatic cholangiocarcinoma refers to biliary tract tumors that arise in the bile ducts outside the gallbladder and the liver parenchyma. For the purposes of this study, this includes patients with hilar and periampullary carcinoma. Approximately 3,000 cases of extrahepatic cholangiocarcinoma are diagnosed in the United States each year.(1) Patients with advanced disease are treated with combination chemotherapy using gemcitabine and cisplatin. The Phase III randomized ABC-02 trial demonstrated a median OS of 11.7 months for patients treated with the combination as compared to 8.1 months for gemcitabine alone. The rate of tumor control (objective response and stable disease for 24 weeks) was 81.4% for the combination.(8) Based upon Phase II data, combination 5-FU based chemotherapy regimens may also be administered. Improved treatment options for this disease would be advantageous to patients.

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. Strong and frequent expression of MSLN has been noted in many solid tumors, but is especially notable in mesothelioma, pancreatic, ovarian, lung and biliary tract malignancies as shown in **Table 1** (adapted from (9)). MSLN expression is also associated with more aggressive disease in pancreatic cancer, cholangiocarcinoma, lung, ovarian and breast cancers (10-14). In pancreatic cancer cell lines, overexpression of MSLN increases proliferation, motility and invasion and decreases survival of mice bearing tumors grown from these cells (15). Similar effects have been seen with other tumor cell types (16-18). These properties make MSLN an attractive target for anti-neoplastic therapies, and more than five anti-MSLN agents are currently undergoing clinical testing.

Table 1. Prevalence of MSLN expression by tumor type(9)

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)
Endometroid	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)

1.2.3 Recombinant Immunotoxins (RITs) that target MSLN

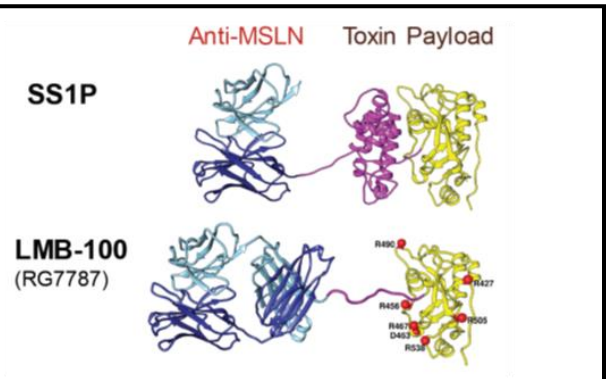
1.2.3.1 Mechanism and structure of RITs

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 the 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 (19).

SS1P was the first MSLN-targeted RIT tested in patients. Phase I studies established a maximum tolerated dose (MTD) of 45 mcg/kg given every other day for three total doses per cycle. Dose limiting toxicities (DLTs) were pleuritis, an expected on-target off-tumor toxicity caused by SS1P-induced inflammation of the normal pleura, and capillary leak syndrome (CLS). Clinical trials have demonstrated that efficacy of SS1P is limited by its immunogenicity. Anti-RIT neutralizing

antibodies (Nabs) form after one cycle in ~90% of patients preventing effective drug exposure in subsequent cycles (20). When SS1P was administered with a lymphocyte-depleting conditioning regimen of pentostatin and cyclophosphamide, this delayed the development of anti-RIT antibodies in most patients. In a pilot study, three of ten patients with chemotherapy refractory mesothelioma achieved durable major responses with this regimen (21). These results provide a proof of principle that RITs can have meaningful clinical efficacy in patients with advanced solid tumors.

Figure 1. RIT Structure



Anti-MSLN antibody fragments are shown in blue. The PE payload contains two domains modified from the native molecule. The majority of Domain II (pink) is deleted from LMB-100. LMB-100 also contain seven point mutations in Domain III (yellow), the catalytic domain, to reduce immunogenicity.

1.2.4 Rationale for the development of LMB-100

LMB-100 (previously RO6927005 and RG7787) is a next generation anti-MSLN RIT developed in NCI's Laboratory of Molecular Biology in collaboration with Roche (**Figure** 1). The anti-MSLN targeting region of LMB-100 uses a humanized Fab fragment instead of the smaller dsFv fragment used in SS1P. In addition, LMB-100 contains a newly engineered PE fragment that has similar or improved activity against most cancer cell lines *in vitro*, and is also much less toxic than SS1P in pre-clinical models while maintaining or improving upon efficacy seen with SS1P in most models (22-25). The new PE contains modifications specifically designed to reduce immunogenicity of the molecule. This includes deletion of a 14 kD sequence that precedes the catalytic domain and 7 point mutations within the catalytic domain itself. These changes ablate the major human B cell epitopes within the molecule and also the most antigenic T cell epitope (26,27).

1.2.5 Nonclinical Studies of LMB-100

1.2.5.1 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 adeno-

squamous 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 un-transfected 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 adeno-squamous lung carcinoma (H596) in severe combined immunodeficient (SCID) beige mice. Three consecutive treatment cycles, given with 1 week breaks in between, led to massive shrinkage of large tumors with an average initial volume of 600 mm^3. Tumor regressions in monotherapy were also achieved when treating subcutaneous xenografts of mesothelioma (NCI-H226), gastric (MKN-28), and triple negative breast (HCC70) cancer cell lines in athymic nude mice. Highly synergistic antitumor efficacy was observed in combination therapy with paclitaxel when treating subcutaneous xenografts of the recombinant high mesothelin expressing 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.

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

1.2.5.3 Toxicology and Safety Pharmacology

The toxicological profile of LMB-100 was assessed after repeated intravenous administration to cynomolgus monkeys, the only relevant species, for a maximum of 5 daily doses for one week or 2 cycles with QOD × 3 dosing, separated by a 9-day dosing free period. Four daily doses of 3 mg/kg exceeded the maximum tolerated dose with animals being found in moribund condition, indicated by clinical signs of hypoactivity, hunched posture, ataxia, and tremors. There were no histopathological changes to account specifically for the deteriorating physical condition of these animals. Histopathological findings such as kidney tubular degeneration/regeneration and changes at serosal-lining tissues were observed at lower doses as well. In general, administration of LMB-100 resulted in both on- and off-target toxicities.

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

The potential of LMB-100 to induce off-target vascular leak in lungs was assessed in female Wistar rats. Mild perivascular edema was reported microscopically but did not correlate with macroscopic or serum chemistry findings consistent with 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.

1.2.6 Rationale for starting dose of LMB-100:

In prior Phase I study, the MTD of LMB-100 was determined to be 140 mcg/kg given as a 30-minute infusion every other day x3. For this combination study, we will decrease the dose of LMB-100 to 100 mcg/kg for initial combination testing. Rationale for limitation to 3 cycles of treatment for Dose Escalation (Arm 1) and Expansion (Arm 2)

Infusion-related reaction (IRR) upon LMB-100 administration is associated with the presence of ADAs. For participant safety, treatment will be limited to 3 cycles to lower risk of IRR if tofacitinib co-treatment is unsuccessful at limiting or delaying ADA development.

1.2.7 Rationale for starting dose and schedule of tofacitinib

Tofacitinib is FDA approved for the treatment of ulcerative colitis at a dose of 10 mg (immediate release formulation) given orally twice daily on a continuous schedule. Tofacitinib will be given at the same dose on this protocol, which is the highest dosage approved by FDA for any indication. For our purpose- diminishing ADA formation- we anticipate that immunosuppression by tofacitinib will only be necessary during the time which immune cells are potentially exposed to LMB-100. Therefore, tofacitinib will not be given continuously. Instead, dosing will be limited to days 1 through 10 of each cycle. This provides immunosuppression throughout the three doses of LMB-100, a lead-in for 3 days before to establish physiologic effect before the first LMB-100 administration, and then continued tofacitinib for 2 days after last administration of LMB-100 for the cycle while the drug is eliminated from the body. Intermittent dosing is anticipated to reduce the risk of infection caused by tofacitinib-mediated immune suppression and hypothetical risk of inhibiting anti-tumor immune response.

1.2.8 Clinical testing of LMB-100

1.2.8.1 Previous Roche study

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

A total of 15 participants were enrolled onto the study before termination. Median age of participants was 60.8 years and 53.3% were female. All participants had received prior anti-cancer therapy for their tumors. Enrolled participants had advanced mesothelioma (7), ovarian cancer (3), pancreatic cancer (3), and gastroesophageal cancer (2). Tumors from 13 of the 15 treated participants 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 2**). 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 2. LMB-100 Dose escalation study- NCT02317419

Dose (mcg/kg)	Number of patients	Patients 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		

1.2.8.1.1 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 3** and **Table 4**) 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 3. Grade 3 or 4 Adverse Events Attributed to LMB-100[1]

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 4. Adverse Events attributed to LMB-100[1]

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**

Dose (mcg/kg)	45	65	100	170	250	**ALL**
# of patients treated	1	1	3	4	4	**13**
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**
Renal Disorders						
Glomerulonephritis minimal	-	-	-	1	-	**1**
Proteinuria	-	-	-	1	1	**2**
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**

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.

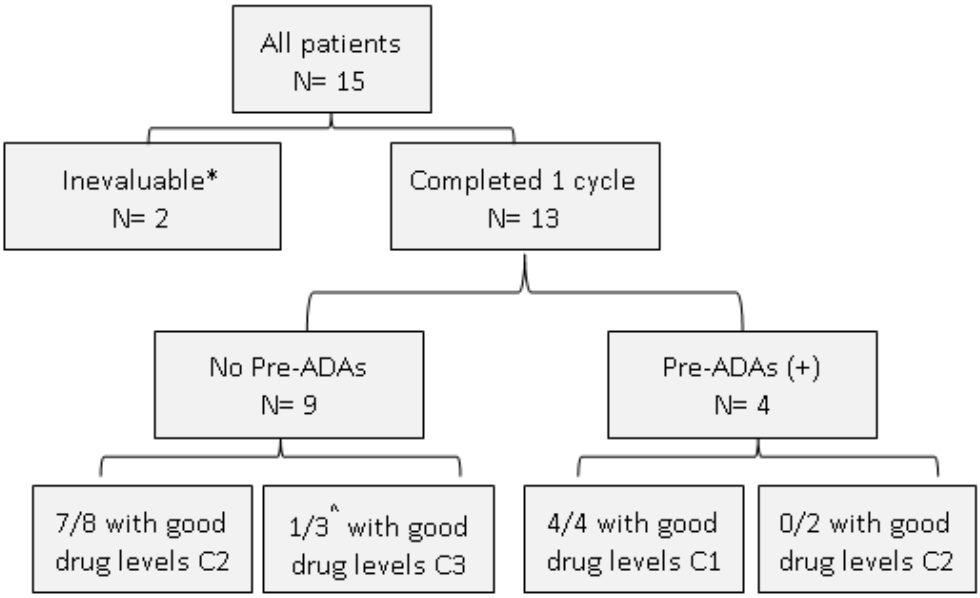
[1] adapted from Clinical Study Report No 1066017 from Roche dated December 2015, "Summary of Adverse Events Related to Study Medication, Safety-Evaluable Patients Protocol: BP29387" See pages 175-193 of the report."

1.2.8.1.2 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 2**.

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 so. 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 5**) In summary these data show that the mere presence of ADAs as measured by the Roche ELISA test is not predictive of ability to achieve measurable LMB-100 concentration in the serum, which is the most important parameter for drug efficacy. However, high titers of ADAs as measured by this test are predictive of diminished LMB-100 serum drug levels, while intermediate or low titers may or may not impact drug levels.

Figure 2. LMB-100 ADAs and Blood Levels



*Roche closed the study before these patients completed their first treatment cycle
^One additional patient has no C3PK data in the record but is recorded as not having progression until C4D1

Table 5. 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	-	-	-	-	-	-

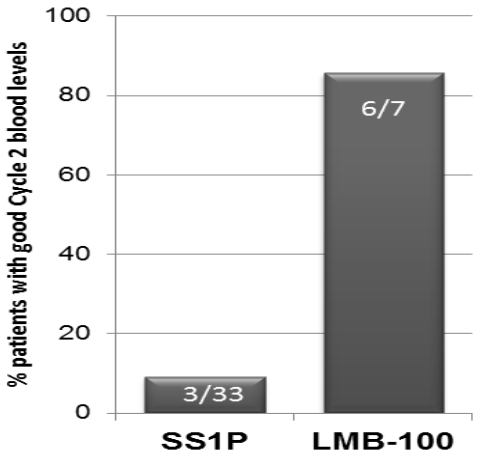
* Patient's treatment stopped due to study closure

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.

1.2.8.1.3 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 3**).

Figure 3: LMB-100 vs SS1P Cycle 2 Blood Levels



1.2.8.2 NCI trials of LMB-100

1.2.8.2.1 Mesothelioma, short infusion

Single agent LMB-100 has been tested in two additional ongoing Phase I studies. A 30-minute infusion given on days 1, 3 and 5 of a 21-day cycle was given to 10 mesothelioma patients (NCT02798536). At 170 mcg/kg, multiple patients experienced reversible acute kidney dysfunction which prolonged hospitalization. For this reason, **single agent MTD of 140 mcg/kg was established**. Toxicities and peak drug levels were similar to the Roche study (manuscript in preparation).

1.2.8.2.2 Combination of LMB-100 with nab-paclitaxel

The LMB-100 has also been tested in both mesothelioma (NCT02798536) and pancreatic cancer patients (NCT02810418) in combination with nab-paclitaxel. In mesothelioma patients, nab-paclitaxel was given at a dose of 100 mg/m^2 on Days 1 and 8. MTD of LMB-100 was found to be 100 mcg/kg/day given over 30 minutes on days 1, 3 and 5 of each 21-day cycle. In pancreatic adenocarcinoma patients, nab-paclitaxel was given at a dose of 125 mg/m^2 on Days 1 and 8. At 100 mcg/kg, DLT of grade 3 myalgia was observed in 2/6 patients. A reduced dose of 65 mcg/kg/day was subsequently tested. DLT of grade 3 edema associated with vascular leak was observed in 1/6 evaluable patients making this the MTD of LMB-100 for the combination. At the MTD, 1/14 patients experienced a partial response as their best response following the maximum 2 cycles of treatment. Grade 4 vascular leak associated with ventricular dysfunction was observed in one patient and the study was closed to further accrual. ADA development is shown in **Table 6**, and was similar to the Roche trial of single agent LMB-100. Evaluation of this combination continues in pancreatic adenocarcinoma patients (manuscripts in preparation).

Table 6: ADA development during LMB-100 treatment

Number of patients with expected serum LMB-100 level				
Treatment	**Study**	**Tumor Type**	**C2**	**C3**
single agent	Roche	MSLN(+)	6 of 9	1 of 3
single agent	NCI	mesothelioma	5 of 10	0 of 9
+NAB-paclitaxel	NCI	mesothelioma	3 of 10	0 of 0
+NAB-paclitaxel	NCI	PDAC	5 of 10	1 of 3
		TOTAL	**19 of 39 49%**	**1 of 13 8%**

1.2.8.2.3 Pancreatic cancer and other MSLN-expressing malignancies, long infusion

Since some pre-clinical studies suggested that duration of exposure to LMB-100 may be more important to anti-tumor activity than peak drug levels (data not shown), a new study was initiated to investigate the safety and efficacy of LMB-100 given in a long infusion format to patients with pancreatic cancer and other mesothelin-positive solid tumor malignancies (NCT02810418). As of

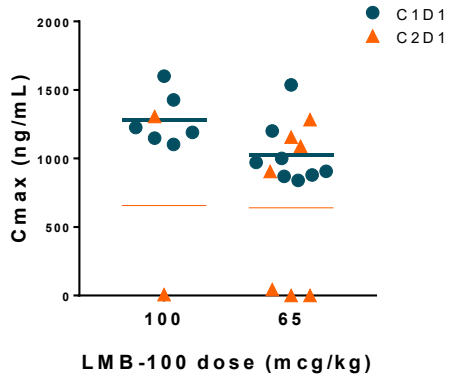
August 2018, 15 participants were enrolled on this study (12 with pancreatic adenocarcinoma, 1 with ampullary cancer, 1 with pleural mesothelioma, 1 with rectal cancer). For this study, patients received only two cycles of study drug by design. Neither toxicity nor efficacy were observed in the 3 patients treated at the initial dose level of 65 mcg/kg/day given over 48 hrs starting on Day 1 of each 21-day cycle. Pharmacokinetic measurements were erratic, likely secondary to inability of the syringe pumps to deliver such small volumes of drug, or due to presence of pre-existing anti-PE antibodies that acted as a drug sink in some patients. In subsequent dose levels, participants were treated with an initial 40 mcg/kg loading dose over 30 minutes prior to the start of the long infusion. **Single agent MTD of 100 mcg/kg/day x48hrs preceded by 40 mcg/kg loading dose was established.** DLT of grade 3 proteinuria was noted in 1/6 patients treated at this dose level. 3/6 patients at this dose level developed non-dose-limiting VLS that included weight gain >5kg, as well as hypotension (grade 2). The dose escalation was halted at this point to consider a more tolerable alternative schedule. Subsequently, a dose of 100 mcg/kg/day x24hrs preceded by 40 mcg/kg loading dose given on days 1 and 4 was tested. Two patients receiving this dose experienced no drug-related toxicity. One additional patient required hold of the D4 dose due to transient grade 2 rise in creatinine, which was considered an investigator-specified DLT. Three additional patients were unable to receive the D4 dose due to medical complications related to their cancer. These 3 patients receiving only the D1 dose also experienced no drug-related DLT or VLS.

Of note, just 1 of 9 patients receiving continuous infusion achieved detectable blood levels of drug with cycle 2 treatment, suggesting that giving LMB-100 in the long infusion format is more immunogenic than the short infusion format. However, 0 of 15 patients have experienced IRR, suggesting that the long infusion reduces the incidence of these reactions.

1.2.8.2.4 Pharmacokinetics of LMB-100

Data from ongoing clinical studies have demonstrated a serum half-life of 61 minutes for LMB-100 as compared to 466 minutes for SS1P (20). It is not known what factors contribute to the longer half-life in circulation of SS1P. In NCI-sponsored studies both with and without nab-paclitaxel, C1 Cmax at 65 mcg/kg, 100 mcg/kg, 140 mcg/kg, and 170 mcg/kg were found to be similar to the values reported during the original Roche Phase I study (**Figure 4**).

Figure 4- Patients with pancreatic adenocarcinoma receiving LMB-100 over 30 minutes with 125 mg/m^2 of nab-paclitaxel on NCT02810418



1.2.9 Administration of tofacitinib for the Prevention of Anti-Drug Antibodies (ADAs)

The development of ADAs against LMB-100 limits the number of effective cycles of RIT that can be administered to 2 or less in almost all patients. The pentostatin + cyclophosphamide (P+C) conditioning regimen represents one clinically validated means to suppress anti-RIT antibody formation, but this strategy has some drawbacks. First, treatment with P+C produces a numeric depletion of lymphocytes that frequently requires months to reverse. This renders patients ineligible for future immunotherapy trials and requires prolonged treatment with prophylactic antibiotics while lymphocyte populations recover. Secondly, nausea and renal dysfunction caused by P+C can reduce patient fitness to tolerate immunotoxin. Thirdly, ADA prevention by co-administration of P+C allows for administration of only one additional effective cycle in most patients (21). Therefore, consideration of other ADA-prevention strategies is warranted.

Tofacitinib is an oral inhibitor of Janus kinases (JAKs) with FDA approved indications for the treatment of rheumatoid arthritis (28), psoriatic arthritis and ulcerative colitis (29). JAKs are non-receptor tyrosine kinases that are activated by cytokine receptors upon cytokine binding. Activated JAKs phosphorylate Signal Transducer and Activator of Transcription (STAT) transcription factors inducing STAT translocation to the nucleus and initiation of new transcriptional programs. Tofacitinib binds and inhibits JAK1, JAK2 and JAK3 with nanomolar affinity resulting in suppression of lymphocyte signaling (30,31). This immunosuppression is rapidly reversible upon drug discontinuation since it does not cause lymphocyte depletion. The most common side effect of tofacitinib is increased risk of viral infection resulting higher incidences of rhinosinusitis and headache and increased cholesterol, which typically begins after 8 weeks of continuous treatment (28,29).

Preclinical data from the LMB immunotoxin group has demonstrated that tofacitinib can prevent anti-SS1P antibody formation in mice repeatedly immunized with this immunotoxin (32). Specifically, continuous administration of tofacitinib to immune-competent mice by osmotic pump infusion (25 ug/h for 28 days) minimized the development of ADAs to repeat immunization with SS1P [**Figure 5**, copied from (32)]. These data support the hypothesis that tofacitinib could suppress development of ADAs in patients treated with LMB-100, allowing patient to receive an increased number of effective cycles of iTox treatment.

Figure 5

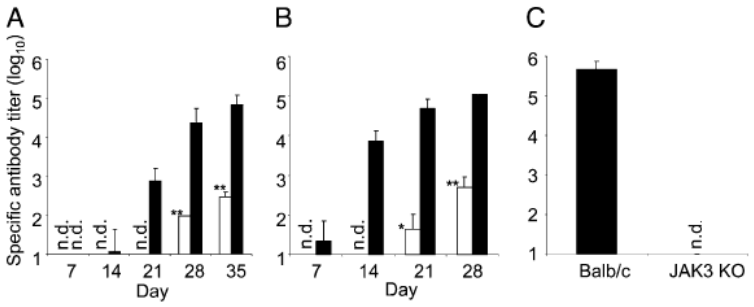


FIGURE 1. Tofacitinib inhibits specific IgG1 Ab responses to immunized proteins in mice. (**A** and **B**) BALB/c mice received tofacitinib (white bars) or vehicle alone (black bars) by osmotic pump infusion and were immunized i.p. every week with 5 μg of SS1P on days 0, 7, 14, 21, and 28 ($n = 8$ per group) (**A**) or with 5 μg of KLH on days 0, 7, 14, and 21 ($n = 5$ per group) (**B**). Before each immunization, sera were collected and tested for anti-SS1P (**A**) or anti-KLH (**B**) Abs by ELISA. Each titration curve was fitted in a four-parameter logistic curve, and the serum dilutions showing 10% of the highest absorbance value of a positive control were taken as the specific Ab titers. Error bars indicate SD. (**C**) JAK3 wild-type mice or JAK3 knockout mice were immunized with SS1P (5 μg) weekly. After 5 wk, sera were taken and anti-SS1P titers were measured by ELISA. Anti-SS1P Ab was not detected in JAK3 knockdown mice by ELISA. Data are expressed as the mean ± SD. $*p < 0.05$, $**p < 0.01$. n.d., not detected in this assay.

1.2.10 Tofacitinib increases serum half-life, delivery to tumor and anti-tumor efficacy of co-administered immunotoxin

In addition to tofacitinib increasing the number of effective cycles of LMB-100 that can be given by limiting ADA formation, we also hypothesize that co-treatment with tofacitinib may increase the efficacy of each individual cycle of LMB-100 treatment. In fact, pre-clinical anti-tumor experiments using the KLM-1 pancreatic cancer and MDA-MB-468 breast cancer murine models showed that co-administration of tofacitinib enhanced anti-tumor efficacy of LMB-100 and also of the anti-transferrin receptor immunotoxin HB21-PE40 in mouse models (**Figure 6**), although anti-tumor activity in cultured tumor cells was not changed.

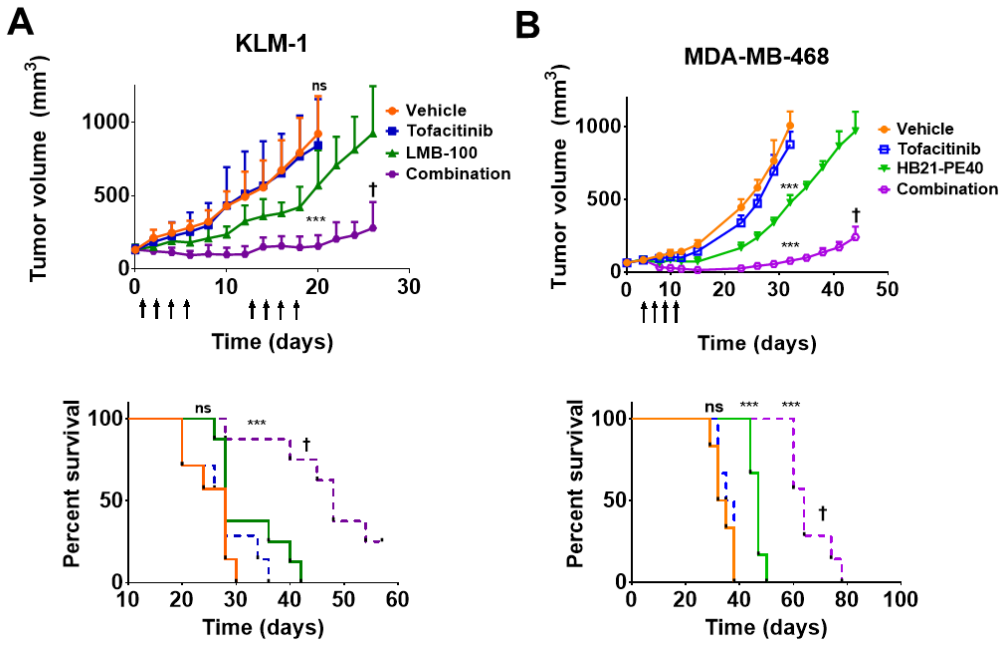


Figure 6: Tofacitinib increased LMB-100 anti-tumor efficacy.
*Athymic nude mice bearing subcutaneous KLM1 pancreatic or MDA-MB-468 breast cancer were treated with immunotoxin LMB-100 (2.5 mg/kg) or HB21-PE40 (0.1 mg/kg) at time points indicated by arrows with or without tofacitinib (5 mg/kg BID). Ns = no significance; ***p < 0.001, D. Fitzgerald lab, in press (JCI Insight)*

Further studies in mice demonstrated that co-administration of tofacitinib increased delivery of fluorescently-labeled immunotoxin to tumor cells (**Figure 7**) and altered immunotoxin pharmacokinetics to prolong serum half-life and increase immunotoxin exposure (**Figure 8**). The mechanism responsible for these changes is under investigation.

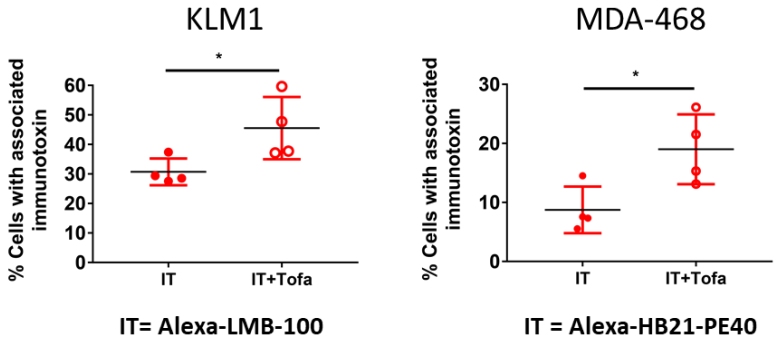


Figure 7: Tofacitinib increased immunotoxin delivery to cancer cells.
*Athymic nude mice bearing subcutaneous KLM1 or MDA-468 tumors were treated with the indicated Alexa-labeled immunotoxin (IT, 2.5 mg/kg) with or without tofacitinib (tofa). Tumors were harvested 3 hours later, cancer cells were dissociated and incorporation of Alexa label was measured by flow cytometry. *p < 0.05. D. Fitzgerald lab, in press (JCI Insight)*

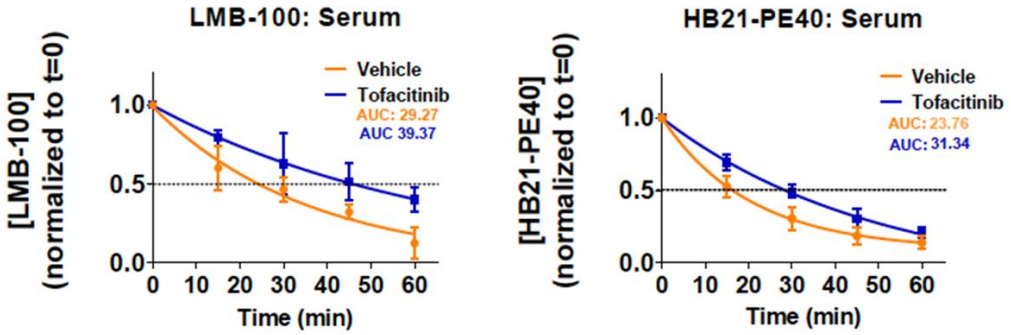


Figure 8: Tofacitinib prolonged immunotoxin half-life in serum.
Athymic nude mice were administered LMB-100 (2.5 mg/kg) or HB21-PE40 (2.5 mg/kg) immunotoxin. Serum taken at indicated time points post-treatment was assessed by assay to determine immunotoxin concentration. AUC = area under the curve. N = 4 mice/ group. D. Fitzgerald lab, in press (JCI Insight).

1.2.11 Lymphocyte signaling suppression by tofacitinib does not enhance tumor growth in mouse model

Tofacitinib suppresses lymphocyte signaling by inhibiting JAKs. Lymphocyte signaling contributes to the anti-tumor immune response and, in fact, higher rates of non-melanoma skin cancers have been observed in patients with autoimmune disease receiving tofacitinib. It is currently not clear how long-term treatment tofacitinib impacts the growth of existing solid tumors. Pre-clinical studies were performed in immune competent mice to assess the effect of tofacitinib on tumor growth. Administration of tofacitinib to Balb-C mice bearing orthotopic 4T-1 murine breast cancer tumors did not increase the rate of tumor growth (**Figure 9**). In addition, the response of these tumors to anti-PD1 immune checkpoint inhibitor therapy was not impacted (Fitzgerald lab, unpublished, data not shown). These experiments suggest that the immunosuppression caused by short-term administration of tofacitinib does not enhance tumor growth.

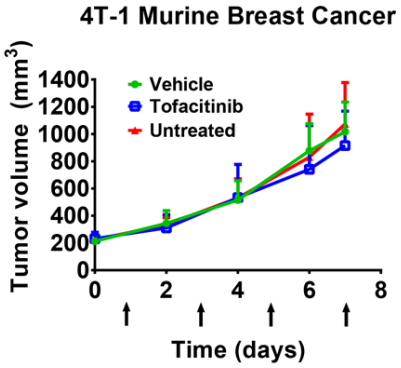


Figure 9: Tofacitinib did not increase 4T-1 xenograft growth.
Balb-C mice bearing orthotopic 4T-1 murine breast tumors were treated with tofacitinib (5 mg/kg BID) at days indicated by arrows. Tumor dimensions were serially measured by digital calipers. N = 10 mice/ group. D. Fitzgerald lab, in press (JCI Insight).

1.2.12 Tofacitinib may increase the risk of venous thromboembolism (VTE) and overall mortality

Post-marketing studies examining long-term effects of chronic daily tofacitinib use in rheumatoid arthritis (RA) and ulcerative colitis patients have suggested that higher dose tofacitinib (10 mg, BID) may increase the risk of VTE. A study of 50,865 patients in the United States observed a trend towards increased incidence of VTE in RA patients taking tofacitinib compared to those taking TNFα inhibitors that was not statistically significant (33). A similar European study (still ongoing and not yet published) which included 7866 RA patients with at least one risk factor for cardiovascular disease found that 10 mg twice daily dose of tofacitinib increased the risk of VTE and overall mortality in patients over age 50 compared to therapy with TNFα inhibitors. Based on these data, the FDA issued a warning and changed package labeling on tofacitinib in July 2019 to advise against the use of tofacitinib in rheumatoid arthritis patients at increased risk for VTE, like cancer patients.

Pancreatic cancer is a highly pro-thrombotic malignancy. Guidelines from ASCO (American Society of Clinical Oncology) and the International Initiative on Thrombosis and Cancer now recommend routine prophylaxis against VTE in all patients with pancreatic cancer receiving systemic therapy who have low risk of bleeding (34,35). Prophylactic anticoagulation may also be recommended to cancer patients with other histologies who are receiving systemic therapy if their Khorana score predicting risk for chemotherapy-associated VTE in the ambulatory setting is ≥ 2 (See **Table 7**).

Table 7: Predictive Model for Chemotherapy-Associated VTE in the Ambulatory Setting (35)

Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1
Prechemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk score ≥ 3 points	
Intermediate-risk score = 1-2 points	
Low-risk score = 0 points	

1.2.13 Rationale for the combination of LMB-100 with tofacitinib

Efficacy of LMB-100 is limited by the formation of ADAs in approximately half of patients before the 2nd cycle of treatment can be administered and almost all patients before a 3rd cycle. Tofacitinib is an FDA approved drug for the treatment of several autoimmune disorders. Based on the preclinical data on the combination of LMB-100 and tofacitinib described in Section **1.2.10**, we hypothesize that co-administration of tofacitinib with LMB-100 will prevent or delay the formation of high titer ADAs to LMB-100, such that more than 2 effective cycles of immunotoxin can be administered to patients. The goal of this clinical trial is to assess the combination for 1) safety and tolerability and 2) immunogenicity.

1.2.14 Rationale for use of mesothelin testing (NSR device)

To be eligible for treatment on study, participants with tumor types other than pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma and epithelioid subtype of mesothelioma are required to have positive mesothelin expression in archival tumor tissue, defined as at least 20% 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 may be eligible for studies with LMB-100 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 Patients must have histologically confirmed solid tumor malignancy for which no curative therapy exists.

2.1.1.2 Pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma or epithelioid subtype of mesothelioma, as determined by NCI Laboratory of Pathology, OR for all other tumor types, at least 20% of tumor cells must express mesothelin. Determination can be made using archival tumor tissue or fresh biopsy if archival tumor tissue is not available.

2.1.1.3 All patients must have evaluable disease (i.e. measurable per RECIST 1.1. or by following CA19-9 tumor marker). Patients in the expansion cohort must have measurable disease, per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.

2.1.1.4 Patients must have received at least one prior standard systemic treatment regimen for advanced disease OR be ineligible to receive available standards due to co-morbidities, prior toxicity, lack of standard options for tumor type, or having received all standards

available for prior treatment of early stage disease OR have refused first-line standard systemic treatment but have received prior anti-cancer treatments.

2.1.1.5 Patients with dMMR/MSI-H disease must have received at least one prior anti-PD1 therapy, be ineligible to receive this treatment due to concurrent medical conditions, or have refused this therapy.

2.1.1.6 ECOG performance status (PS) 0-2 (**Appendix A-** Performance Status Criteria).

2.1.1.7 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of LMB-100 alone or in combination with tofacitinib in persons with <18 years of age, children are excluded from this study.

2.1.1.8 Patients 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 and 14 days from radiation therapy, systemic treatments (such as chemotherapy), or experimental drug treatment. All acute toxicities from prior treatment must have resolved to grade 1 or less except alopecia, anemia, peripheral neuropathy, or endocrinopathies corrected by replacement therapy.

2.1.1.9 Adequate hematological function: neutrophil count of ≥ 1.5×10^3 cells/μL, platelet count of ≥ 85,000/μL, hemoglobin ≥ 9 g/dL

2.1.1.10 Serum albumin ≥ 2.5 mg/dL without intravenous supplementation

2.1.1.11 Adequate liver function: Bilirubin <2.5 x ULN for all, AST and ALT < 3 x ULN except for patients with significant tumor burden in their liver where AST and ALT < 5x ULN is acceptable in the absence of other etiologies for transaminitis

2.1.1.12 Adequate renal function: creatinine clearance [Estimating glomerular filtration rate (EGFR) method or measured] ≥ 50 mL/min. Measured clearance will be used if both numbers are available.

2.1.1.13 Must have left ventricular ejection fraction ≥ 50%

2.1.1.14 Must have an ambulatory oxygen saturation of > 88% on room air

2.1.1.15 The expansion phase patients must meet all eligibility criteria above (from **2.1.1.1** to **2.1.1.15**) AND must have diagnosis of pancreatic adenocarcinoma or extrahepatic cholangiocarcinoma with pathology confirmed to be consistent with one of these diagnoses by NCI Laboratory of Pathology.

2.1.1.16 The effects of LMB-100 alone or in combination with tofacitinib 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.

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

2.1.2 Exclusion Criteria

2.1.2.1 Known or clinically suspected CNS primary tumors or metastases including leptomeningeal metastases as CNS penetration of LMB-100 is expected to be poor. CNS

metastases are permitted if they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days.

2.1.2.2 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).

2.1.2.3 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 a life expectancy of less than 6 months as judged by the investigator.

2.1.2.4 Contraindication to receiving prophylactic doses of low-molecular weight heparin (LMWH) or direct oral anticoagulants (DOAC) such as current active bleeding (except for grade 1 hematuria or epistaxis), recent history of significant bleeding without subsequent effective medical or surgical intervention, known history of gastric varices, uncontrolled malignant hypertension, history of coagulopathy that confers increased risk of bleeding. Patients on concurrent treatment with anti-platelet agents such as aspirin or clopidogrel are eligible if deemed to have acceptable risk of bleeding in consultation with Hematologist. Patients already receiving prophylactic or therapeutic doses of anticoagulant (heparin-based or DOAC) for at least 4 weeks with no indication of significant bleeding while on therapy are considered NOT to have a contraindication to this therapy.

2.1.2.5 Inability to administer or unwillingness to comply with recommended VTE prophylaxis for the duration of study treatment.

2.1.2.6 Prior diagnosis of hematologic malignancy

2.1.2.7 Active or uncontrolled infections (including tuberculosis, HIV, HBV, or HCV) or reasonable clinical suspicion of an active infection (such as cholangitis) as tofacitinib suppresses lymphocyte signaling and will impair host response to infection

2.1.2.8 Latent TB infection as identified by interferon-ɤ release assay (IGRA). If IGRA is indeterminate, tuberculin skin test (TST) may be used to determine status.

2.1.2.9 Live attenuated vaccinations within 14 days prior to treatment.

2.1.2.10 Use of a strong inhibitor or inducer of CYP3A4 within 14 days prior to enrollment (see **Flockhart Table** (https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx) or similarly updated source for a list of such agents)

2.1.2.11 Inability to take or digest oral medication.

2.1.2.12 Dementia or altered mental status that would prohibit informed consent.

2.1.2.13 Pregnant women are excluded from this study because the effects of LMB-100 and/or tofacitinib 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

and/or tofacitinib, breastfeeding should be discontinued if the mother is treated with either of these agents.

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

2.1.2.15 Participants with contra-indication and/or history of severe hypersensitivity reactions to any components related to LMB-100 and tofacitinib.

2.1.2.16 Patients who have previously received LMB-100 (and therefore have high-levels of pre-existing ADA's to drug)

2.1.3 Recruitment Strategies

Information about the study will be posted on sites such as clinicaltrials.gov and the CCR recruitment website. Information about the trial will also be distributed on NIH social media platforms. Subjects will also be drawn from patients seen in OP12 Medical Oncology clinic at the NIH Clinical Center as well as from referrals from outside providers.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

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

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

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

For patients requiring testing for MSLN expression (see Section **2.3.1**), screening will occur on this study. For all other subjects, screening will occur on study 01-C-0129.

The following activities will be performed only after the subject has signed the appropriate consent for screening. They will be performed within 28 days before registration for study treatment unless specified:

- Assess tumor MSLN expression by immunohistochemistry analysis in archival tissue or fresh biopsy samples ONLY for patients who do not have a diagnosis of epithelioid mesothelioma, extrahepatic cholangiocarcinoma or pancreatic adenocarcinoma.
- Medical History and physical exam
- Vital signs including ambulatory oxygen saturation by pulse oximetry
- ECOG performance status
- Pregnancy test in women of childbearing potential (within 7-days prior to initiation of study therapy)
- ECG
- Echocardiogram
- CT scan of chest, abdomen and/or pelvis and areas of known or suspected disease involvement; MRI and/ or PET scan may also be performed when appropriate per PI discretion.
- 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, 1,25-dihydroxy vitamin D, Coagulation (PT, PTT), lactate dehydrogenase
- CA 19-9 serum tumor marker for pancreatobiliary cancer patients, or other appropriate tumor marker in other tumor types
- Testing for HIV, HCV, HBV: anti-HIV antibody, Anti-HCV Antibody, HBs Ag Screening
- Screening for latent tuberculosis by interferon-ɤ release assay: QuantiFERON-TB Gold Plus or similar
- Urinalysis

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

2.3.1 Subjects that require pre-screening for MSLN

Participants that do not have pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma or epithelioid mesothelioma must undergo pre-screening for MSLN expression.

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

2.4 TREATMENT ASSIGNMENT PROCEDURES

Cohorts

Number	Name	Description
1	Dose Escalation	1-6 patients per level x2 dose levels
2	Dose Expansion	Up to 15 additional eligible and evaluable patients will be treated to assess the safety of optimal dose for patients with pancreatic cancer or extrahepatic cholangiocarcinoma

Arms

Number	Name	Description
1	Dose Escalation	LMB-100 (escalating doses) + tofacitinib for 3 cycles
2	Dose Expansion	LMB-100 + tofacitinib (at dose determined in dose escalation portion of the study) for 3 cycles. At least 8 subjects must have PDAC.

Arm Assignment

Patients in Cohort 1 will be directly assigned to Arm 1. Patients in Cohort 2 will be directly assigned to Arm 2.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

Schema

- This is a Phase I study which will accrue up to 45 participants.
- Participants will be admitted to the NIH Clinical Center for LMB-100 administration.
- For the dose escalation phase, a 3+3 dose escalation will be used. Two dose levels are planned. A minus dose level could be utilized if de-escalation is necessary.
- Following identification of an optimal dose and schedule, an expansion phase of 15 participants will be initiated at the optimal dose for patients with pancreatic adenocarcinoma and extrahepatic cholangiocarcinoma. At least 8 participants in the expansion phase must have pancreatic adenocarcinoma.
- Participants on the Dose Escalation and Dose Expansion Arms will be treated for a maximum of 3 cycles with the exception described in the next bullet
- Participants on the Dose Escalation and Dose Expansion Arms who appear to be deriving clinical benefit may continue to receive treatment beyond 3 cycles as indicated in Section Error! Reference source not found..

- Toxicities and adverse events will be monitored continuously during treatment and for 30 days beyond the last treatment.

3.1.1 Dose Limiting Toxicity

For the study, a DLT will be defined as any of the following events occurring during the first cycle of treatment (21 days), the DLT evaluation period. Toxicities determined to be unequivocally related to disease progression or intercurrent illness will not be regarded as DLTs. The following will be considered DLTs:

- Any death not clearly due to the underlying disease or extraneous causes
- Transaminitis that meets criteria for Hy's Law: grade ≥2 elevation of AST or ALT with simultaneous elevation of total bilirubin to ≥ 2x ULN while alkaline phosphatase remains < 2x ULN.

Hematological toxicities:

- Grade 4 neutropenia (i.e. absolute neutrophil count (ANC) <0.5 x 10^3 cells/μL for a minimum duration of 7 days)
- Grade 3 and 4 febrile neutropenia (i.e. ANC < 1.0 x10^3 cells/μL with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour; or life-threatening consequences with urgent intervention indicated)
- Grade 4 thrombocytopenia (≤25.0 x10^3 cells/μL)
- Grade 3 thrombocytopenia associated with bleeding episodes
- Grade 4 anemia

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

- Grade 3 nausea and vomiting lasting <48 hours occurring in the absence of appropriate anti-emetic treatment
- Grade 3 diarrhea lasting for ≤ 2 days with no fever or dehydration
- Infusion-related reactions **up to and including Grade 3**. IRRs are not considered to be DLTs since, based on experience with monoclonal antibodies, they are idiosyncratic and not dose-related events. Precautions will be taken if IRRs Grade ≥2 occur (see Section **3.3**).
- Asymptomatic grade 3 elevation of ALT, AST, GGT, bilirubin or alkaline phosphatase attributable to study drug that persists for less than 7 days if not violating Hy's Law. (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 after LMB-100 infusion and resolving within 48 hours to ≤ Grade 2 and fully resolved within 1 week.

Other toxicities:

- Any other drug related toxicity considered significant enough to be qualified as a DLT in the opinion of the principal investigator.
- Inability to start cycle 2 within 2 weeks after completing cycle 1 due to drug-related adverse events.

If a participant experiences a DLT of any grade, the investigator will have the option to either stop treatment or to resume the treatment at the next lowest dose level based on best clinical judgment. Patients will be assessed based on the original cohort. 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.

3.1.2 Dose Schedule

The dose schedule is outlined below in **Table 8**. Patients will be enrolled as per standard 3+3 design, if 0 of 3 or <2 of 6 patients experience DLT then dose escalation may proceed. If 2 or more patients experience DLT at any dose level, then dose de-escalation is required.

The rule by which clinical team will decide when to escalate or de-escalate have been explained in **Table 9.**

Table 8

Dose Level	**LMB-100 infusion (mcg/kg) Given days 4, 6, 8**
Level -1	65
Level 1	**100**
Level 2	140

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

*All patients will receive tofacitinib 10 mg BID on days 1-10 of each cycle

Dose escalation will follow the rules outlined in **Table 9**.

Table 9

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to five additional patients will be entered at the next lowest dose level to complete a max cohort of 6.
1 out of 3	Per PI discretion, follow instructions for $\geq$ 2 DLT OR Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to five additional patients will be entered at the next lowest dose level to complete a max cohort of 6.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

3.1.3 Treatment Extension

Participants who complete 3 cycles of therapy with LMB-100/tofacitinib and appear to be deriving clinical benefit as evidenced by lack of progression on CT scan and decreasing serum tumor marker (in patients with serum tumor marker that has historically followed their disease trend) may continue to receive additional cycles of treatment at the discretion of the PI until unacceptable toxicity or patient is no longer thought to be benefiting, or PI's decision to discontinue treatment. If a participant is offered treatment extension but refuses, he/she will be removed from protocol therapy. Participants offered treatment extension may defer immediate treatment with study drugs to take a treatment holiday or to receive other intervening treatments (including investigational treatments). If a participant chooses to defer treatment extension beyond 6 weeks or to have a different intervening therapy, the PI may require to repeat some screening safety evaluations before reinitiating LMB-100/tofacitinib and will require washout periods and criteria consistent with those described in Sections **2.1.1.8**, **2.1.1.9** and **2.1.1.10**. Safety monitoring while receiving treatment extension will continue as described in the **Study Calendar**. Limited research labs will be taken as described in Sample Collection Schedule (Section **5.2**).

3.2 DRUG ADMINISTRATION

Appendix B-Model chemotherapy note provides a sample chemotherapy note describing the regimen.

3.2.1 Tofacitinib

Tofacitinib will be administered orally twice daily on days 1 -10 of each cycle by the participant while at home and by nursing if the participant is admitted to the inpatient unit. A diary (see **Appendix C-** Patient Medication Diary) will be kept to document dose, date and time of day the drug was dosed. If a participant vomits after taking tofacitinib, then no action is required; the participant should simply take the next dose of tofacitinib as scheduled. If a participant omits/ skips a dose, the participant should take the dose as soon as possible and contact the study team for instruction on when to administer the next dose.

3.2.1.1 VTE prophylaxis for patients receiving tofacitinib

VTE prophylaxis will be provided to all patients on study who are not already on treatment with appropriate anticoagulant (note that Vitamin K inhibitors are NOT considered appropriate therapy in this patient population) as per criteria below:

Patients with Khorana Score < 2 will receive enoxaparin 40 mg subcutaneous daily beginning Day 1 and continuing until 24 hrs after the last dose of tofacitinib for each cycle (Day 11 unless tofacitinib is discontinued early). Patients with contraindication to enoxaparin (e.g. prior history of heparin-induced thrombocytopenia or inability to perform subcutaneous injection) may instead receive another regimen (see **Table 10**).

Patients with Khorana Score ≥ 2 (including all pancreatic cancer and extrahepatic cholangiocarcinoma patients) will be initiated on prophylactic anticoagulation therapy throughout treatment (from Cycle 1 Day 1 until 14 days post the last dose of the study medications tofacitinib and LMB-100) as per ASCO guidelines (35). List of appropriate therapies for prophylaxis that are on CCR formulary are shown below in **Table 10** . Choice of therapy should be based upon patient preference, concurrent medications, bleeding risk/ tumor type, renal function, and ability to take and digest oral medication.

Table 10: Prophylaxis for VTE in Ambulatory Cancer Patients Receiving Outpatient or Inpatient Systemic Therapy (Khorana Score ≥ 2)

enoxaparin	40 mg subcutaneous injection once daily
rivaroxaban	10 mg by mouth once daily
apixaban	2.5 mg by mouth twice daily

3.2.2 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.

LMB-100 will be given as a ~30-minute infusion on days 4, 6 and 8 (QOD x3) each 21-day cycle.

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. For this study, participants will be admitted to the NIH Clinical Center for LMB-100 administration.

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

3.2.2.1 General Instructions

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

3.2.2.2 Specific Instructions

LMB-100 is diluted with 0.9% Sodium Chloride Injection, USP (0.9% NaCl) **in-line** immediately prior to administration (see **Figure 10** below).

The undiluted LMB-100 drug product (DP) is administered by intravenous infusion using a disposable syringe and syringe driver pump. So as not to compromise drug product physico-chemical stability, dilution with 0.9% NaCl will 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 10**).

The pump used to administer 0.9% NaCl will be programmed at 9-times the hourly rate of LMB-100 in order to deliver LMB-100 at a concentration of 0.1 mg/mL. An IV infusion pump and syringe driver should be used to control the infusion rates for 0.9% NaCl solution and LMB-100, respectively.

LMB-100 is administered either peripherally or centrally through a patient's vascular access device. If there is no pre-existing central vascular access device and peripheral access is inadequate, a central access device will be installed.

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 within a biological safety cabinet with appropriate personal protective garb to contain and minimize exposure to the drug product under conditions of inadvertent release.
2. Transfer from LMB-100 product vials to a syringe a volume of LMB-100 appropriate for a patient's dose *PLUS* 3 mL excess volume to prime the extension tubing and filter set that will be attached to the syringe (see step 3).
3. Attach to the syringe (first) an extension tubing set (e.g., medex REF MX448HL60) and (second) a filter set with pore size within the range of 0.2- to 0.22-µm (e.g., medex REF MX448HF). The syringe with extension set and filter set attached is "the syringe assembly".
4. Prime the syringe assembly tubing with LMB-100 from the syringe and cap it with a closing cone/stopper (e.g., Spinning Spiros® connector or comparable closed system transfer device cap).
5. The syringe assembly should be stored under refrigeration (2°– 8°C; 35.6° – 46.4°F) until it is used.
6. Chemical and physical in-use stability for LMB-100 drug product in syringes has been demonstrated for 24 hours at 2°–8°C and 24 hours at ambient temperature (not >25°C; 77°F). The LMB-100 drug product does not contain antimicrobial preservatives; LMB-100 solution will be transferred to syringes under appropriate aseptic conditions and should be used immediately. If not used immediately, total in-use storage times of prepared syringes for infusion should not exceed 24 hours when stored under refrigeration.
7. Attach (spike) the 0.9% NaCl container (bag) with an administration set. Attach the distal end of the administration set to the most distal port on a 4-way stopcock (or two 3-way stopcocks connected end-to-end), and prime the tubing and stopcock with 0.9% NaCl.
8. Attach the stopcock to the patient's vascular access device.
9. Undiluted LMB-100 will be filtered during administration before it is diluted in-line with 0.9% NaCl (see **Figure 10**). Place the syringe containing LMB-100 in the pre-programmed syringe driver, remove any caps or closures from the end of the syringe assembly and attach the syringe assembly tubing to the stopcock/manifold at the port closest to a patient's vascular access device.
10. Start the pump driver for 0.9% NaCl to establish line patency and unimpeded flow BEFORE starting to administer LMB-100 with the syringe pump.
11. When 0.9% NaCl flow is established, start the syringe pump to administer LMB-100.
12. The end of infusion is defined as the time point at which the syringe driver finishes administering the total volume of LMB-100 to be infused.
13. In case of any adverse events related to the infusion, please refer to the specific recommendation described in Section **3.3.1**.

14. The line for drawing blood for LMB-100 PK samples should be placed in the opposite extremity from the one with the infusion line in patients who do not have a mediport.

3.2.2.3 Monitoring

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 at 30, 60 and 120 minutes (±15 minutes) from the end of the infusion (EOI). Vital signs pre-infusion, EOI, and 120 minutes post-EOI must be captured in the eCRF. Other vital signs measurements are not required to be captured in the eCRF unless abnormalities are observed.

3.2.2.4 Standard Pre-medication for Participants Receiving LMB-100

Due to the prevalence of infusion related reactions (IRRs) seen in previous studies of LMB-100, all patients will be pre-medicated 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 PRN (when necessary) should be physically available in the infusion unit in case of severe IRR during LMB-100 administration.

Note: An alternative histamine H2 antagonist may be substituted for PO ranitidine such as IV ranitidine or famotidine 20 mg PO or IV if the preferred pre-medication is unavailable.

Pre-medication should be given 30-60 minutes prior to LMB-100 infusion.

3.2.2.4.1 Additional Precautions for administration of LMB-100 in patients with IRR during LMB-100

Participants receiving LMB-100 who have experienced an IRR of Grade 2 to 4 during a previous infusion despite standard pre-mediation should also receive:

- Dexamethasone 8 mg IV, 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 where dexamethasone or another steroid was pre-administered should not receive further LMB-100 and will be discontinued from study therapy.

Table 11. Pre-medications for LMB-100

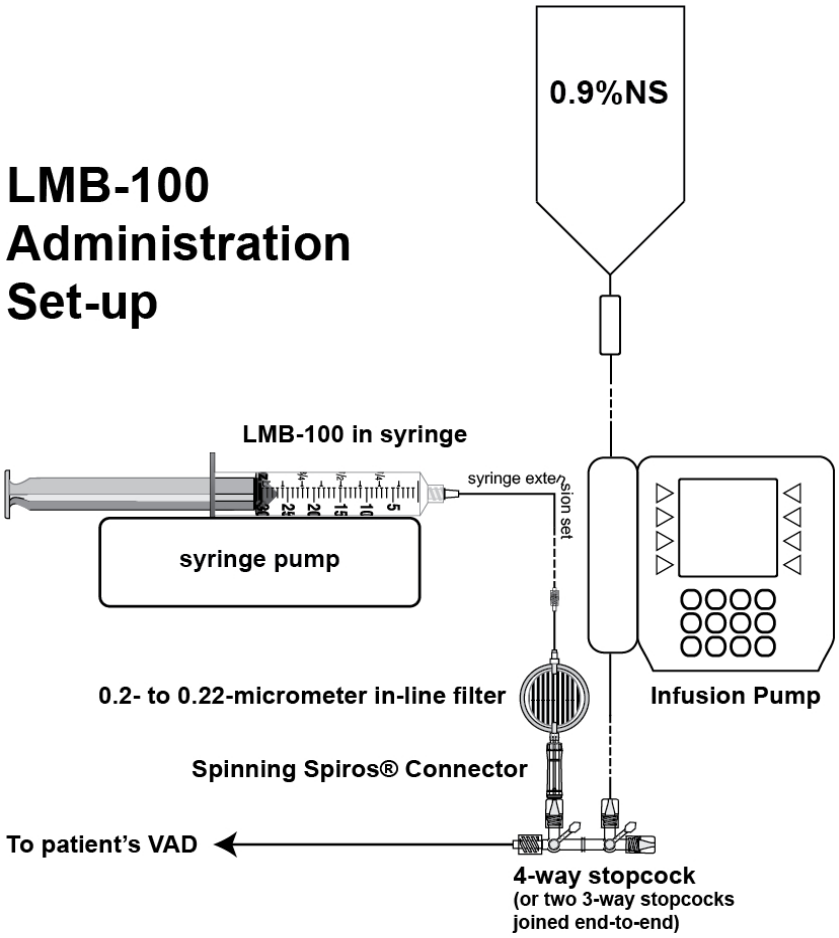
	Dose (mg)	Route
Acetaminophen	650	PO
Diphenhydramine	25-50	PO or IV
Ranitidine[#]	150	PO
Dexamethasone*	8	IV

*Given only in case of prior IRR

[#] IV ranitidine or famotidine 20 mg PO or IV are allowed if the preferred pre-medication is unavailable.

3.2.3 Schematic view of the administration set-up

Figure 10



3.3 DOSE MODIFICATIONS

3.3.1 LMB-100

LMB-100 infusion may be held for up to 48 hours due to drug-associated toxicity or adverse events from other intercurrent medical conditions (such as primary cancer diagnosis) that resolve with or without medical intervention to grade 1 or less within this time frame. Toxicities for which further LMB-100 treatment should NOT be given are stated below in **Table 12,** which also provides guideline on how to manage some toxicities anticipated with LMB-100.

Table 12. Guidelines for Managing LMB-100 Adverse Events

Event	Action to Be Taken
IRR/hypersensitivity reaction during administration of LMB-100	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. If the infusion is interrupted: • In the event of IRR CTCAE Grade1, upon resolution of symptoms, the infusion will resume at 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. • In the event of IRR CTCAE Grade 3 or Grade 4 (which may include pulmonary or cardiac events) or an anaphylactic reaction, the infusion should not be restarted, and the participant should receive aggressive treatment • Participants experiencing IRR CTCAE Grade 4 or anaphylaxis must be permanently discontinued from study treatment For participants receiving 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: o Dexamethasone (20 mg PO 6 -12hrs before infusion or 8 mg IV, 30 – 90 min before infusion) or equivalent dose of another corticosteroid as clinically indicated
Capillary leak syndrome (CLS) For Grade 1-3 Capillary leak syndrome, the symptoms that make up this syndrome will be recorded separately, instead of classifying them as CLS. If the PI determines that the symptoms meet the definition of Grade 4 or 5 CLS, they will be recorded separately and CLS Grade 4 or 5 will also be recorded.	In the event of Grade 4 CTCAE capillary leak syndrome (urgent intervention indicated): o Vasopressor support (e.g., phenylephrine) if indicated to stabilize blood pressure o 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 o For pulmonary congestion provide diuretic and/or albumin treatment as appropriate o Progressive shortness of breath may require endotracheal intubation or drainage of a pleural effusion o For oliguria and /or rising serum creatinine level delay LMB-100 if Grade 3 urine output decrease (<10 mL/hr)

Event	Action to Be Taken
	○ Use dopamine if participant is unresponsive to or unable to tolerate fluids ○ Manage pericardial effusion as outlined in section on "Inflammatory reactions to serosal membranes" below
Inflammatory reactions to serosal membranes	○ Hydrocortisone (200 mg IV) or a glucocorticoid equivalent 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) permanently discontinue LMB-100 treatment. Consult cardiology service for management recommendations which may include pericardial drainage. ○ 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 participants to maintain oral hydration (~1.5 L/ day)
Nausea	Ondansetron or another anti-emetic should be available as needed
Renal toxicity	In the event of Grade 1 or greater renal toxicity consider increasing oral or intravenous hydration, and consider delaying LMB-100 administration by up to 48hrs. In the event of Grade 2 or greater renal toxicity hold LMB-100 administration until recovery to Grade 1 or better. If this does not occur within 48hrs, no further LMB-100 should be given during the cycle.
IRR = infusion related reaction; IV = intravenous; CTCAE = Common Terminology Criteria for Adverse Events	

3.3.2 Dose Adjustment of tofacitinib

Tofacitinib dose should be reduced for infection, hepatic impairment, myelosuppression or other events as per package insert. Dose modifications will be based on the package insert recommendations for ulcerative colitis and should be followed for renal impairment, hepatic impairment, lymphopenia, neutropenia, anemia, and in patients taking strong or moderate CYP3A4 inhibitors (as can be found here: **Flockhart Table** or in another frequently updated source).

If VTE prophylaxis medication is missed or held for more than 3 days (e.g. in case of renal impairment or procedure like tumor biopsy), then tofacitinib should be held until anticoagulation can be restarted.

3.3.3 Schedule Modifications When Study Drugs must be Held

If a patient begins treatment with tofacitinib but is unable to receive any planned dose of LMB-100 on schedule due to medical or other complications unrelated to tofacitinib treatment:

- For delays in LMB-100 administration anticipated to be ≤ 48 hrs, tofacitinib should be continued. LMB-100 administration should resume within the 48-hour window. Tofacitinib treatment should be extended so that patients continue to receive tofacitinib treatment for two days beyond the last LMB-100 infusion
- For delays lasting or anticipated to last >48hrs, tofacitinib treatment should be stopped.

When tofacitinib is stopped mid-cycle due to medical or other complications related or unrelated to tofacitinib:

- If any LMB-100 was administered, the remaining doses of LMB-100 may be given with or without restart of tofacitinib, per investigator's discretion. If tofacitinib is restarted, it should be continued for two days beyond the last LMB-100 infusion

If no LMB-100 was administered, the cycle is aborted. Patients have 4 weeks from the date of the last tofacitinib dose to restart (from Day 1) the planned schedule for the cycle. No more than 2 cycles may be aborted and restarted. If Cycle 1 treatment is aborted and baseline imaging studies to assess tumor burden (CT CAP or other) were performed >28 days before cycle restart, then baseline imaging studies should be repeated prior to first LMB-100 dose of the restarted cycle. Baseline tumor biopsy should not be repeated.

3.4 STUDY CALENDAR

Unless otherwise specified, screening assessments must occur within 28 days prior to registration for study treatment. **Cycle 1, day 1 assessments may occur up to 7 days prior to treatment initiation.** If screening tests were performed within this window, then they do not need to be repeated on C1D1. Dosing cycles may be delayed for up to one week or started up to 2 days early to accommodate schedule conflicts, federal holidays and inclement weather, etc. They may be delayed for up to two weeks due to toxicity. There is no time limit on dosing cycle delays for patients receiving treatment extension.

Procedure	**Screening**	**All Cycles (21 days)**								**Post Therapy**	
		Day 1	Day 3*	Day 4	Day 6	Day 8	Day 9	Day 15	Day 21	Safety Follow Up Visit[7]	Long Term Follow Up[11]
Tofacitinib		administered BID days 1-10 of each cycle									
Prophylactic anti-coagulation		Khorana Score < 2: administer daily on days 1-11 of each cycle Khorana Score ≥ 2: administer throughout treatment until 14 days after last dose of tofacitinib/ LMB-100									
LMB-100				X	X	X					
History and PE	X	C1 only	X		X	X				X	
Weight			X		X	X	C1 only			X	
Height			C1 only								
Vital signs[1]	X	C1 only	X	X	X	X	C1 only			X	
ECOG Performance Status	X	C1 only	X							X	
Labs[2]	X	C1 only	X		X	X		C1 only[14]	C1 only[14]	X	
D-dimer		C1 only	X			X					
Cholesterol Panel		C1 only								X	
TBNK		C1 only	C1 and C3 only				C1 only				
1,25-dihydroxy Vit D	X									X	

Procedure	**Screening**	**All Cycles (21 days)**								**Post Therapy**	
		Day 1	Day 3*	Day 4	Day 6	Day 8	Day 9	Day 15	Day 21	Safety Follow Up Visit[7]	Long Term Follow Up[11]
Hepatitis and HIV screening panel	X										
IGRA	X										
Urinalysis	X		X		X	X				X	
Urine albumin and creatinine	C1 only		C1 only		C1 only	C1 only					
Pregnancy test[3]	X		X								
Confirmation of Dx[4]	X										
Assessment of tumor MSLN expression[4,5]	X										
CT CAP and/or MRI[8]	X	After 3 cycles of study treatment (from 7 days post-treatment completion)								X	X
CA 19-9 or appropriate tumor-specific marker[5]			X							X	
Doppler U/S of bilateral lower extremities		Optional[15]									
ECG	X		C1 only			C1 only				X	
Echocardiogram	X										
Ambulatory Oxygen Saturation	X										
Chest X-ray			X[9]								
NIH Advance Directives Form[6]		C1 only[6]									
Biopsy	X[13]	C1 only[12]	C2 only[12]								

Procedure	**Screening**	**All Cycles (21 days)**								**Post Therapy**	
		Day 1	Day 3*	Day 4	Day 6	Day 8	Day 9	Day 15	Day 21	Safety Follow Up Visit[7]	Long Term Follow Up[11]
PKs	Please refer to Section **5.2**										
Correlative Studies	Please refer to Section **5.2**										
Annual phone call to monitor survival and additional CA therapy											X
Adverse events[10]		Monitored continuously									
Concomitant meds		Monitored continuously									

*If not performed on day 3, may be performed on day 4 prior to the start of LMB-100 infusion

[1] Vital signs including temperature, blood pressure, pulse rate, and oxygen saturation should be recorded on the indicated days. In addition, systolic blood pressure, pulse rate, and oxygen saturation must be monitored pre-infusion, every 15 minutes (± 5 minutes) during the infusion, at end of infusion (EOI), then 30, 60 and 120 minutes (±15 minutes) following EOI.

[2] CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, C-reactive protein (CRP), Creatine Kinase (CK), PT, PTT, LDH. PT and PTT will be done only at the time of screening, Day 1 of each cycle, and within 24hrs prior to biopsies (if biopsy will be performed).

[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] Applicable only to patients on dose escalation with tumor types other than pancreatic adenocarcinoma, extrahepatic cholangiocarcinoma, or epithelioid subtype of mesothelioma

[6] As indicated in Section **11.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably prior to beginning treatment 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] Safety follow up will occur 3 – 6 weeks after last dose of study therapy. If the patient is unable to return to the clinic for the follow up visit, an adverse event assessment will be performed by telephone.

[8] Scans, every ~9 weeks, will only be performed until disease progression. Note: for patients on long term follow up, scans may be performed outside of NIH. Gadolinium will be used for MRI in patients where MRI is required.

[9] Chest x-ray on cycle 1 only for patients with existing mediport. Chest x-ray is required with each cycle to confirm placement of a central line if placement is required for drug administration.

[10] Adverse events will be monitored continuously for 30 days beyond the last treatment.

[11] Study visits after safety follow up visit will be encouraged but not required. Only patients who are removed from study therapy for reasons other than disease progression will be invited to return to clinic (approximately every 6 weeks) for the indicated scans and labs until disease progression. All patients will be followed until death through phone contact for overall survival.

[12] Optional at cycle 1 day 1 and cycle 2 day 3.

[13] Only if archival tumor tissue is not available

[14] +/- 1 day

[15] Should not be performed in patients on daily systemic anticoagulation prior to study enrollment / start. May be performed up to 14 days before or 3 days after cycle 1 day 1.

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. Criteria for removal from protocol therapy

- Completion of study therapy
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Pregnancy
- Unacceptable Toxicity as defined in Sections **3.1.1** and **3.3**
- Requirement for any of the prohibited medications listed in Section **4.1.2**
- Investigator discretion

3.5.1 Off-Study Criteria

- Completed study follow-up period
- Decision to end the study
- Participant requests to be withdrawn from study
- Death

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

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

- Any other investigational therapy
- Cytotoxic chemotherapy agents other than study agents
- Radiotherapy. Note: palliative radiotherapy is allowed.

- Strong inhibitors or inducers of CYP3A4 (as can be found here: **Flockhart Table** or in another frequently updated source)
- Any medications or treatments that may adversely affect the immune system such as allergy injections, immune globulin, interferon, immunomodulators, cytotoxic drugs, or systemic corticosteroids (oral or injectable) at doses higher than needed for adrenal replacement (except as specified as part of protocol treatment).
- Other systemic anti-neoplastic agents and targeted therapies
- Live vaccines

If any anti-neoplastic or investigational therapies listed above are needed, the patient 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.

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 pre-treatment PK assessment may be drawn from the line that will be used to administer LMB-100. 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 K_2EDTA 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, but not required as samples are stable at 4°C for up to 24 hours.

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

5.1.1.4 Sample storage

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

5.1.2 Assessment of LMB-100 anti-drug antibodies (ADAs)

5.1.2.1 Sample Collection

Samples will be collected before the first dose of LMB-100 during each cycle as per Section **5.2**.

Draw 2mL into K_2EDTA tube (purple top). Samples should be inverted 8 to 10 times after collection. Store on wet ice or at 4°C. Processing within 60 minutes of blood collection is highly preferred.

5.1.2.2 Sample Processing, Shipping and Storing

Samples will be processed in the Clinical Pharmacology Program as described in Section **5.1.1.2** and autoantibody levels will be retrospectively assessed. Samples will be shipped as described in Section **5.1.1.3** and stored as described in Section **5.1.1.4**.

5.1.3 Cytokines and circulating endothelial cells (CECs) for identification of a mechanism for PE-mediated capillary leak syndrome (CLS)

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 (36). *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 (37). 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 blood from participants. Levels of a panel of cytokines known to affect the vasculature will be assessed. Change in cytokine levels from baseline will be compared.

In addition, circulating endothelial progenitor cells (CEP) and mature circulating endothelial cells (CEC) will be collected to assess endothelial cell dynamics (see Section **5.2** for specific time points). These cells 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.

5.1.3.1 Specimen collection- cytokine analysis

Plasma and serum will be collected from participants on the days and time points shown in Sections **5.2**.

Draw 2mL into K_2EDTA tube (purple top). Samples should be inverted 8 to 10 times after collection. Store on wet ice or at 4°C. Samples must be processed within 120 minutes of blood collection due to instability of some analytes.

Draw 2mL into SST tube (red top).

5.1.3.2 Sample processing- cytokine analysis

Samples will be processed in the Clinical Pharmacology Program as described in Section **5.1.1.2**.

Upon arrival in the CPP, each plasma sample (K_2EDTA tube) 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. Immediately transfer plasma specimen (maintaining samples at 4°C throughout handling process) to 2mL cryovials and store at -70°C.

Upon arrival in the CPP, each serum sample (SST tube) should be processed in the following manner:

1. Store at room temperature for 15-30 minutes to allow blood to clot
2. Centrifuge at 1500xg for 10 minutes at 4°C to remove clot
3. Immediately transfer serum specimen (maintaining samples at 4°C throughout handling process) to 2mL cryovials and store at -70°C.

5.1.3.3 Sample Storage- cytokine analysis

Samples will be stored in the CPP. Deidentified samples will be transferred to the Alewine laboratory for analysis within 12 months of freezing.

5.1.3.4 Sample Collection- CECs

Draw blood into one 8-cc CPT citrate (BD) tube as specified in Section **5.2**

5.1.3.5 Sample Processing-CECs

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel- trepelj@mail.nih.gov; Min-Jung- Lee-leemj@mail.nih.gov; and Sunmin Lee- leesun@mail.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240 760 6330and a lab member will pick up the sample.

5.1.4 To evaluate changes in the tumor microenvironment following treatment with LMB-100 and tofacitinib

We hypothesize that tofacitinib and LMB-100 will alter the tumor microenvironment. Pre-clinical studies have shown that tofacitinib treatment depletes levels of some immune cells within tumors. We will perform intrapatient comparison of tumor tissue before and after treatment. These samples will be assessed for change in 1) volume of stroma versus tumor cells, 2) volume, density and architecture of collagen and other matrix proteins, 3) density of tumor blood vessels, 4) tumor MSLN expression, 4) infiltration of immune cells, and 5) PD-L1 expression by the tumor.

5.1.4.1 Specimen collection, preparation and storage

Tumor biopsy specimens will be obtained when feasible with patient consent. Specimens will be processed and stored by NCI Laboratory of pathology and presence of tumor confirmed.

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 Peripheral blood immune gene expression

Peripheral blood mononuclear cells (PBMC) will be assessed by the Trepel Lab 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.

Peripheral blood immune gene expression will be evaluated by the Trepel Lab using the NanoString nCounter® platform (NanoString Technologies, Seattle, WA). Collect peripheral whole blood in a PAXgene Blood RNA tube (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions. After the whole 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.

5.1.6.1 Sample Collection

Draw blood into one 8-cc CPT citrate (BD) tube at (1) baseline, just prior to beginning therapy, (2) cycle 1 following end of last infusion as specified in Section **5.2**, and (3) cycle 2 day 1, prior

to therapy. Draw blood into two one 2.5 ml PAXgene RNA tube at (1) baseline, just prior to beginning therapy, and (2) cycle 2 day 1, prior to therapy.

5.1.6.2 Sample Processing

Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel- trepelj@mail.nih.gov; Min-Jung Lee- min-jung.lee@nih.gov; and Sunmin Lee- leesun@mail.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.

5.2 SAMPLE COLLECTION SCHEDULE

Cycle	Day	LMB-100 PKs 5.1.1	ADA 5.1.2	Plasma & Serum Cytokines 5.1.3	CECs 5.1.3	Immune Subsets 5.1.6	Immune gene expression 5.1.6	Tumor Sample 5.1.4, 5.1.5
		2 mL K_2EDTA tube	2 mL K_2EDTA tube	2 mL K_2EDTA and SST tubes	two 8-cc CPT citrate (BD) tubes		2.5 mL PAX gene RNA tube	N/A
Screening								X[a]
1	1[b]		Pre-tofacitinib	Pre-tofacitinib		Pre-tofacitinib	Pre-tofacitinib	X[0]
	4	Pre-, EOI, then 1, 2, 4, 8-10, 12-16 hrs post-LMB-100	Pre-dose LMB-100[c]	Pre-dose, EOI, 4hrs post-LMB-100	Pre-dose LMB-100	Pre-dose LMB-100		
	8	Pre-, EOI LMB-100						
	9			X	X	X	X	
≥2	3		X[c]					
	4	Pre-, EOI LMB-100 C3 only: 1, 2, 4, 8-10, 12-16 hrs post-LMB-100		pre-LMB-100	C2 only: pre-LMB-100	C2 only: pre-LMB-100		
	8	Pre-, EOI LMB-100		EOI LMB-100				X[d]
Treatment Extension	4	Pre-, EOI LMB-100	pre-LMB-100					
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; CEC=circulating endothelial cell

a. Archival tissue collection permitted if tissue was collected within 1 month of completion of last treatment or biopsy if no tissue available.
b. May be drawn up to 7 days prior
c. May be drawn on day 3 or 4 before LMB-100 administration
d. Cycle 2 only. May be obtained on any one of Days 4-8.

C1D1 (within 7 days prior to treatment): optional biopsy.

Note: Timed samples scheduled for EOI must be drawn within 5 minutes of this reference point. Those scheduled within 4hrs of EOI should be collected within +/- 20 minutes of indicated time.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

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

5.3.1 Clinical Pharmacology Program

Upon arrival in the Clinical Pharmacology Program (CPP), OCD, CCR, NCI, all samples are barcoded, with data entered and stored in Labmatrix, the system utilized by the CPP. This is a secure program, with access to the Labmatrix system limited to defined CPP personnel, who are issued individual user accounts. Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle, time point, dose, material type, as well as box and freezer location. There are patient demographics that can be obtained to correlate with the samples through Labmatrix. 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 Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per 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. If additional studies are to be performed on any samples retaining patient identifiers, obtained during the conduct of this trial, a Request to Conduct Research for Stored Human Samples Specimens, or Data Collected in a Terminated NCI-IRB Protocol will be submitted. Otherwise, access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. If specimens are to be discarded at any point, they will be disposed of in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested). The PI will report any loss or unanticipated destruction of samples per Section **7.2**.

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 record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section 7.2.

5.3.5 NCI Laboratory of Pathology

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

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

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

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

Document AEs from the first study intervention, Study Day 1, through the end of the treatment. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

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, this will be reported expeditiously per requirements in Section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

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

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

How and where will the data be shared?

Data will be shared through:

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

When will the data be shared?

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

6.2.2 Genomic Data Sharing Plan

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

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. 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 evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).(38) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For pleural mesothelioma, modified RECIST for MPM (malignant pleural mesothelioma)(39) should be used as described in Section **6.3.9.**

6.3.1 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 patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated

and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

6.3.2 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.(40-42) 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.(43)

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.

6.3.3 Response Criteria

6.3.3.1 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.

6.3.3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

6.3.3.3 Evaluation of Best Overall Response

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

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

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 patients with partial response or complete response.

6.3.7 Disease Control Rate

Disease control rate (DCR) is defined as the percentage of patients with partial response, complete response, or stable disease.

6.3.8 Overall Survival

Overall survival (OS) is defined as the length of time from start of treatment until death from any cause.

6.3.9 Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) lesions are difficult to measure reliably.(39) Therefore, modified criteria were defined in 2004 adjusting target lesion measurements to the specific needs of this disease.

6.3.9.1 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.

6.3.9.2 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.

6.4 TOXICITY CRITERIA

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

7 NIH REPORTING REQUIREMENTS / DATA SAFETY MONITORING PLAN

7.1 DEFINITIONS

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

7.2 OHSRP Office of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

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

7.3 NCI Clinical Director Reporting

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

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

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

7.4 NIH required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

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

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

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

7.4.2 Safety Monitoring Committee (SMC)

This protocol will protocol will be periodically reviewed by an intramural 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 every 6 months as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the

study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

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.

7.4.3 Independent Monitoring Committee (IMC)

The protocol will also have an Independent Monitoring Committee (IMC), consisting of the Principal Investigator and two independent, qualified investigators who are outside of the Laboratory of Molecular Biology (LMB) branch and are not involved in the study. The committee will meet after the first 5 subjects have been treated and completed the DLT evaluation window. The IMC will review adverse events and other associated safety data (this review may occur prior to the first annual continuing review date). The committee will be responsible for deciding whether treatment can proceed under the current protocol, whether protocol modifications are required for study continuation, or whether the protocol should be closed to further accrual due to toxicity of the study agents. The IMC may be convened for an ad hoc evaluation of protocol safety by the Principal Investigator or at the request of the IRB or SMC at other occasions during the study if concerns about study drug or research protocol safety or toxicity arise.

The minutes of the IMC meetings will be submitted to the IRB at the time of continuing review, unless an issue arises that requires prompt reporting to the IRB and then results will be submitted more expeditiously.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

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

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization

- A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
- A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

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

8.1.4 Severity

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

8.1.5 Relationship to Study Product

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

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

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

8.2 Assessment of Safety Events

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

occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

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

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

8.3 Reporting of Serious Adverse Events

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

All SAE reporting must include the elements described in Section **8.2**.

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

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

8.4 Reporting Pregnancy

8.4.1 Maternal exposure

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

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

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

8.4.2 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 study drugs.

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.

8.5 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected in expedited manner to the FDA in accordance to 21 CFR 31.2.32. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

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

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

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

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

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

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary Endpoints

The primary endpoint of the dose escalation phase is to identify the MTD and the desirable dose of LMB-100 with tofacitinib.

The primary endpoint of the expansion phase is to determine the number of participants that meet a threshold serum drug concentration during cycle 2 of treatment. The threshold drug level has been set at >600 ng/mL as measured at EOI for any LMB-100 administration during the cycle of interest.

10.1.2 Secondary Endpoints

The secondary endpoints for both the dose expansion and dose escalation cohorts are the LMB-100 peak serum level, half-life and AUC during cycle 1, and the percentage of participants with EOI LMB-100 serum drug concentration that meets threshold during cycle 3. For the dose escalation cohort, the percentage of participants with EOI LMB-100 serum drug concentration that meets threshold during cycle 2 of treatment will also be measured. For the dose expansion cohort, the number and description of adverse events by grade will also be reported.

10.2 SAMPLE SIZE DETERMINATION

The primary endpoints of this trial are to 1) identify the MTD and the desirable dose of the tofacitinib + LMB-100 combination format and 2) to determine whether the combination results in 80% of patients achieving threshold drug levels during cycle 2 of LMB-100. The MTD is defined as the maximum dose at which less than 33% of patients experience a DLT. The desirable dose will be selected from among the dose levels at or below the MTD. A lower dose than the MTD might be assessed in the expansion phase if chronic toxicity of LMB-100 is judged to be intolerable by the investigator at the MTD.

As per standard 3+3 design, if 0 of 3 or <2 of 6 patients experience DLT then dose escalation may proceed. If 2 or more patients experience DLT at any dose level, then dose de-escalation is required.

Dose escalation will proceed from dose level 1 to 2. If 0 of 3 or 0-1 of the first 6 patients in dose level 1 have a DLT, then dose escalation will proceed to dose level 2. Alternatively, if 2 or more patients in level 1 experience DLT, then dose will be de-escalated to dose level -1.

Based on two dose levels, the theoretical maximum number of subjects that can enroll on the dose escalation would be 12 (6 patients per level x2 dose levels).

Following completion of the dose escalation, enrollment of an additional 15 patients with pancreatic cancer or extrahepatic cholangiocarcinoma will be undertaken to better assess the a) safety of the optimal dose in the target population, and b) ability of tofacitinib to delay development of ADAs against LMB-100 and result in serum LMB-100 drug levels reaching threshold in cycle 2 and beyond. Participants on the dose escalation arm who are treated at MTD and meet eligibility requirements for the dose expansion phase can be counted towards the 15 patients needed to accrue to the expansion phase. We estimate that as many as 50% of patients

who start treatment will develop progressive disease by restaging after 2 cycles and would therefore be uninformative for assessing the longer-term immunogenicity endpoint. Thus, additional patients may be needed to complete the evaluation of toxicity and possible efficacy at the escalating dose levels.

This evaluation in 15 patients of either histology (but at least 8 patients in this expansion phase must have pancreatic adenocarcinoma) will be undertaken using the following guidelines: The objective will be to determine if the fraction of patients who are able to achieve threshold levels of LMB-100 in cycle 2 is consistent with 80% and greater than 50%. If 15 evaluable patients are enrolled, and if 11 or more patients meet threshold drug levels in cycle 2, then the probability of this occurring is 5.9% if the true probability of achieving threshold drug levels in cycle 2 were 50% and the probability of this occurring is 83.6% if the true probability of achieving threshold drug levels in cycle 2 were 80%. Thus, the expansion phase would be considered to have a positive outcome if 11 or more of 15 patients in the expansion phase achieve threshold drug levels. In practice, after the trial has ended accrual, the fraction of evaluable patients assessed during the expansion phase that achieve threshold drug levels in cycle 2 will be determined and reported along with two-sided 80% and 95% confidence intervals to aid in interpretation of the results. The fraction of patients who achieve threshold drug levels in cycle 3 will also be reported along with a 95% confidence interval, but this may be a small fraction and will be interpreted as being an exploratory evaluation.

As an early stopping rule, if after the first 5 evaluable patients in the expansion cohort have been treated, 0 of the 5 achieve threshold drug levels in cycle 2, then no further patients will be accrued as soon as that can be determined, with no pause in accrual, since this would be inconsistent with the goal of having 11 or more of 15 patients achieving threshold drug levels in cycle 2.

With up to 12 patients in the dose escalation phase and 15 in the expansion cohort, a maximum of 27 evaluable patients are required to complete accrual to this study. The accrual ceiling will be set at 45 patients to account for screen failures or patients who are treated but unable to complete the DLT period. It is anticipated that up to two patients per month may enroll onto this trial. Thus, accrual is expected be completed in approximately 2 years.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

All patients who receive treatment during dose escalation will be reported. Any patient who receives any study drug treatment and experiences a DLT related to study drug within 21 days of initial treatment is evaluable. Otherwise, patients evaluable for DLT must: 1) receive all doses of study drugs, 2) be followed for study drug toxicity for at least 21 days after the administration of the first dose of LMB-100.

In the expansion phase, up to 15 evaluable patients who can have their drug levels assessed in cycle 2 will be included in analyses. Up to 5 patients will be replaced if they have PD before C2, but if more than 5 patients progress before C2, then no further patients will be accrued as soon as this can be determined.

10.3.2 Evaluable for objective response:

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.) Responses or progressions noted in patients receiving treatment extension will be recorded in the study database but will not be reported in the aggregate objective response rate, which only corresponds to assessments taken prior to the start of a 4^{th} cycle.

10.3.3 Evaluable Non-Target Disease Response:

Patients who have lesions or tumor marker 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 or increase in tumor marker.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The DLTs among patients enrolled during the dose escalation phase will be determined and reported at each dose level. In the expansion phase, the fraction of evaluable patients who have achieved threshold drug levels in cycle 2 will be reported.

10.4.2 Analysis of the Primary Endpoints

The DLTs among patients enrolled during the dose escalation phase will be determined and reported at each dose level.

In the expansion phase, the fraction of evaluable patients who meet the endpoint drug level threshold in cycle 2 will be reported along with two-sided 80% and 95% confidence intervals to aid in interpretation of the results.

10.4.3 Analysis of the Secondary Endpoint(s)

The secondary endpoints are the number and description of adverse events by grade in the expansion cohort. For both dose escalation and expansion cohorts secondary endpoints include: the LMB-100 peak serum level and half-life and AUC during cycle 1. Each of these will be reported using descriptive measures such as percentages and counts as appropriate. For both dose escalation and dose expansion cohorts, we will report the percentage of patients who have formation of neutralizing anti-LMB-100 ADAs affecting drug concentration during cycle 2 and cycle 3.

10.4.4 Safety Analyses

Safety will be evaluated during the dose escalation phase and will include reporting toxicities by grade and type at each dose level in addition to DLTs.

During the 15-patient expansion cohort, the following rule will be used: Within the initial 6 patients, no more than 1 patient in 6 is permitted to experience a DLT attributable to study agents. After the initial 6 patients, safety will be monitored continuously per the following rule: if the cumulative fraction of patients enrolled who experience a DLT attributable to study agents is 1/6 or less, patients will be allowed to continue to enroll onto this protocol.

10.4.5 Baseline Descriptive Statistics

Demographic and clinical characteristics of all patients will be reported.

10.4.6 Planned Interim Analyses

As an early stopping rule, if after the first 5 evaluable patients have been treated, 0 of the 5 meet threshold drug levels in cycle 2, then no further patients will be accrued since this is inconsistent with the goal of having 11 or more of 15 meeting threshold drug levels. Accrual will not be halted while awaiting the determination of drug levels in cycle 2 based on 5 patients; thus, additional patients may begin treatment while this determination is being made.

10.4.7 Sub-Group Analyses

In the expansion cohort, the fraction of patients meeting threshold drug levels in cycle 2 will be analyzed as an exploratory endpoint according to pancreatic adenocarcinoma vs. extra-hepatic cholangiocarcinoma history.

10.4.8 Tabulation of individual Participant Data

None will be provided

10.4.9 Exploratory Analyses

The following are the intended exploratory analyses focusing on the patients in the expansion cohort:

Disease control rate (DCR) at 9 weeks will be estimated along with a 95% confidence interval. PFS and OS will be estimated by the Kaplan-Meier method, along with 95% confidence intervals. Changes in appropriate tumor markers with treatment (if applicable to patient's tumor type) will be determined and tested for change from baseline using a Wilcoxon signed rank test. Titer of free anti-LMB-100 antibodies at the start of each cycle and following completion of treatment will be obtained and results reported descriptively; the relationship of these values with peak serum drug levels of LMB-100 will be explored. Association of response with tumor MSLN expression will be done by comparing levels between responders and non-responders using an appropriate non-parametric test such as a Cochran-Armitage test or Fisher's exact test. Changes in circulating endothelial cells following immunotoxin treatment, changes in serum cytokines following immunotoxin treatment, and changes in tumor microenvironment following immunotoxin treatment will be reported descriptively, with statistical testing of changes as appropriate. Any statistical tests performed on the exploratory endpoints will have results presented without formal adjustment but interpreted in the context of the number of tests performed. In patients receiving treatment extension, the anti-drug antibodies and peak plasma LMB-100 drug levels will be obtained at each cycle after cycle 3 and reported with descriptive statistics. The levels of these

measures after cycle 3 may be compared descriptively to those in earlier cycles for purposes of evaluating the effect of the agent in this small subset of patients.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

LMB-100 targets the cell surface antigen MSLN and is ineffective against tumor or normal cells that lack MSLN. Many different solid tumor types express MSLN such as mesothelioma, pancreatic, colorectal and lung adenocarcinomas, epithelial ovarian cancers, cholangiocarcinomas, gastric and triple negative breast cancers, as well as some tumors of squamous cell origin. At advanced stages, these tumors are incurable although standard therapies can improve duration of survival and symptoms. There is an unmet need to identify improved and less toxic therapies in these patient populations. Given the overall poor prognosis of these patients, particularly after progression of tumor on or after initial treatment regimen(s), the potential to directly benefit from treatment outweighs the risks of participating in the study.

All patients meeting the criteria listed in Section **2.1** are eligible for enrollment.

11.2 PARTICIPATION OF CHILDREN

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

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

11.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

11.4.1.1 Risks from Study Drugs

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

assessments, 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 agent as discussed in Section **12**.

11.4.1.2 Blood Collection

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

11.4.1.3 Image Guided Biopsy Collection

The risks of the research biopsies collected at screening, at cycle 1 day 1, and on day 3 of cycle 2 include pain, bleeding and infection at the biopsy site.

11.4.1.4 Risks of exposure to ionizing radiation

This research involves up to 6 CT C/A/P scans, up to 3 chest X-ray, and up to 3 CT-guide biopsies per year. Subjects will be exposed to up to approximately 9.18 rem. This level of exposure is associated with an increased risk of cancer.

11.4.1.5 MR Imaging

MRI is a standard of care test for some patients with pancreatic and cholangiocarcinoma. The risks of MR imaging are relatively small.

The US Food and Drug Administration has issued warnings that administration of gadolinium (updated September 9, 2010), the MRI contrast imaging agent used in this protocol, has been associated with development of a disease called **nephrogenic systemic fibrosis (NSF)**. The syndrome is rare (approximately 600 cases reported worldwide as of September 2010, out of several million administrations of gadolinium), but disabling and in some cases, fatal. All cases to date have occurred in patients with severe renal disease, including patients on dialysis. NSF has been nearly eradicated secondary to careful screening of renal function and avoiding use of gadolinium in patients with eGFR <30 ml/min/1.73 BSA. Even in patients with end stage renal disease, there have been only rare occurrences of NSF because of precautions taken to use more stable contrast agents at lower doses. This protocol excludes patients with renal insufficiency (eGFR <50 ml/min). The FDA has issued warnings in 2017 and 2018 that some gadolinium may be retained in the brain, bone and skin although health risks of accumulation have not been reported to date. In accordance with the FDA Drug Safety Communication of 05/16/2018, the Medication Guide for gadobutrol (or other macrocyclic gadolinium contrast agent if applicable) will be made available to all subjects with scans that will involve gadolinium-based contrast agent administration.

11.4.1.6 Central Line Insertion

Patients without a mediport in whom peripheral access cannot be obtained can have a central line placed for treatment administration. 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.

11.4.2 Benefits

Patients with many different solid tumor types expressing MSLN are in continuous need of improved therapy options, particularly patients with pancreatic and biliary adenocarcinomas, the

focus population of this clinical trial. Preclinical data has demonstrated promising anti-tumor efficacy of LMB-100 in xenograft models in monotherapy and combination therapy. Laboratory studies have demonstrated that tofacitinib inhibits the development of antibodies against LMB-100. Therefore, LMB-100 + tofacitinib may improve clinical outcome of patients with mesothelin-expressing tumors. Several clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines.

11.5 CONSENT PROCESS AND DOCUMENTATION

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

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

12 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

12.1 LMB-100 (IND # 123332)

12.1.1 Source

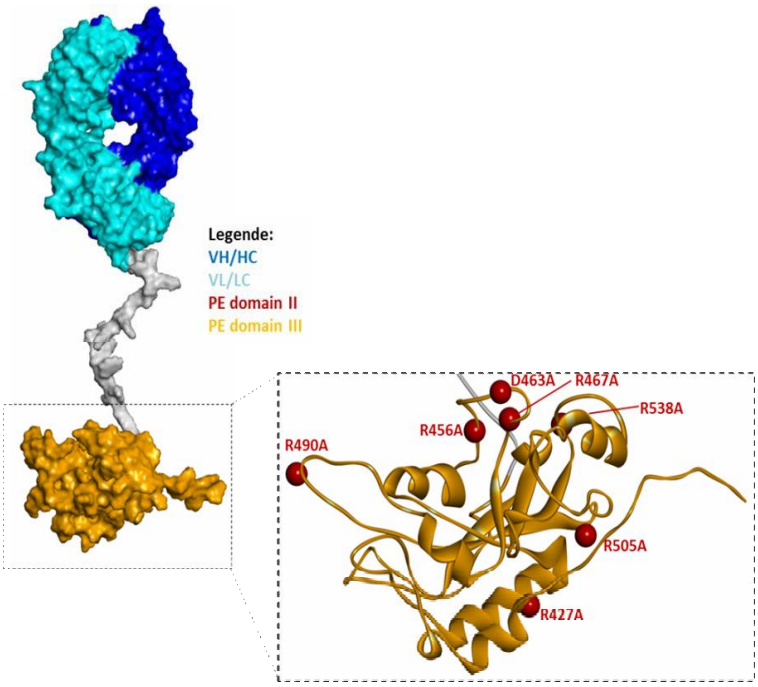
LMB-100 was transferred to the NIH CC Pharmacy by Selecta Biosciences, the drug manufacturer. For this trial, the drug will be supplied by the NIH CC Pharmacy.

12.1.1.1 Mechanism of action

LMB-100 is a novel recombinant anti-mesothelin targeted cytolytic fusion protein (cFP) developed for the treatment of patients with solid tumors that express the mesothelin protein. Mesothelin is a suitable candidate for targeted therapy due to its very limited expression in normal/non-malignant tissue and its high expression in several tumor entities including mesothelioma, ovarian cancer, pancreatic cancer, gastric cancer, breast cancer, and lung cancer. To target mesothelin, a humanized Fab fragment of the anti-mesothelin antibody SS1 is linked to a truncated and de-immunized recombinant 24 kD fragment of Pseudomonas exotoxin (PE24). After binding to mesothelin, the complex is internalized by endocytosis and kills cells by inhibition of eukaryotic elongation factor 2 (eEF2), leading to arrest of protein synthesis and secondarily triggering cell death by apoptosis or necrosis.

12.1.1.2 Molecular Weight: approximately 73 kDa

12.1.1.3 Chemical Structure



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

12.1.2 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.

12.1.2.1 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 (Please refer to Sections **1.2.8** and **3.3.1** for details). 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.

12.1.2.2 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.(20)

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.

12.1.2.3 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.

12.1.2.4 Risk of Capillary 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.

12.1.2.5 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.

12.1.2.6 Risk of Cardiac Toxicity

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

12.1.2.7 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.

12.1.2.8 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.

12.1.3 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.

12.1.4 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.

12.1.5 Administration procedures

Please refer to Section **3.2.2**.

12.1.6 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.

12.2 TOFACITINIB

Please refer to the FDA-approved package insert for product information, and a comprehensive list of adverse events.

12.2.1 Source

Tofacitinib is commercially available in 5 and 10 mg tablets. Immediate release formulation will be used for this protocol.

12.2.2 Administration

Oral

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14 APPENDICES

14.1 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.

14.2 APPENDIX B-MODEL CHEMOTHERAPY NOTE

Bolded text should be replaced with patient-specific information.

(1)
Tofacitinib, 10 mg PO bid, Days 1-10

(2)
LMB-100: <**dose per schema**> mcg/kg, IV on Days 4, 6, 8 given over 30 minutes

- Run with 1:10 in-line dilution of normal saline = **<mg LMB-100>** * 18 = **# ml/hr**

LMB-100 dose for patients weighing more than 100 kg will be calculated as if they weigh 100kg.

Pre-medications to be given 30-60 minutes prior to LMB-100

- Diphenhydramine 25-50 mg PO or IV
- Ranitidine 150 mg PO (see **Table 11** for alternative formulations)
- 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 L daily while receiving LMB-100.

14.3 APPENDIX C- PATIENT MEDICATION DIARY

		Cycle #_____ Patient Name_____ Patient Study ID _____
		INSTRUCTIONS TO THE PATIENT: 1. Complete one form for each Cycle. 2. You will take 1 pill of 10 mg tofacitinib in the morning and also 1 pill of 10 mg tofacitinib in the evening each day. Do not crush or chew. 3. Record the date and what time you took them. 4. If you have any comments or notice any side effects, please record them in the Comments column. 5. Please bring your pill bottles and this form to your physician when you go for your next appointment. 6. If a dose is missed, log this in Comments column and call the Study Team for instructions on what to do. Do not take additional doses to make up missed dose unless instructed to do so by the study team.

Date	**Day**	**Tofacitinib** (taken twice a day)		
		Time (AM)	**Time (PM)**	**Comments (side effects or missed doses)**
	1			
	2			
	3			
	4			

	5			
	6			
	7			
	8			
	9			
	10			

Patient's Signature: _____ Date: _____

Staff Signature: _____Date: _____