Protocol Number:	SGNLVA-002
Version:	Amendment 11; 19-Oct-2023
Protocol Title:	Single Arm, Open Label Phase 1b/2 Study of SGN-LIV1A in Combination with Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer
Investigational Drug:	Ladiratuzumab Vedotin (LV; SGN-LIV1A)
Phase:	1b/2
IND Number:	117532
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PROTOCOL SYNOPSIS

Protocol Number SGNLVA-002 **Version** Amendment 11; 19-Oct-2023 **Phase** 1b/2	**Product Name** Ladiratuzumab Vedotin (LV; SGN-LIV1A) **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

Single Arm, Open Label Phase 1b/2 Study of SGN-LIV1A in Combination with Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer

Study Objectives

Primary

Evaluate the safety and tolerability of the combination of ladiratuzumab vedotin (LV; SGN-LIV1A) and pembrolizumab in patients with locally-advanced or metastatic triple-negative breast cancer (LA/M TNBC)

Identify the recommended dose and schedule of LV in combination with pembrolizumab in patients with LA/M TNBC

Evaluate the confirmed objective response rate (ORR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of the combination of LV and pembrolizumab in patients with LA/M TNBC

Secondary

Evaluate duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) as measured by RECIST v1.1

Evaluate overall survival (OS)

Exploratory

Evaluate ORR, DOR, DCR, and PFS as measured by Immune Response Evaluation Criteria in Solid Tumors (iRECIST)

Assess pharmacokinetics (PK) and incidence of antitherapeutic antibodies (ATAs) of LV

Evaluate programmed death ligand 1 (PD-L1) and LIV-1 expression-response relationships

Assess exploratory biomarkers (e.g., in the tumor immune microenvironment or periphery) of study treatment-mediated pharmacodynamic effects

Study Population

Eligible patients are at least 18 years of age with unresectable LA/M, histologically documented TNBC (estrogen receptor [ER]/progesterone receptor [PR]/human epidermal growth factor receptor 2 [HER2]-negative) who have not previously received cytotoxic therapy for treatment of unresectable LA/M breast cancer (BC). Parts A – C **do not** require preselection based on PD-L1 status; however, for Part D only, eligible patients must have a PD-L1 combined positive score (CPS) <10. A minimum of 6 months must have elapsed after any prior treatments given with curative intent. Though tumor expression of LIV-1 is not required for enrollment, fresh tumor tissue is required across all parts of the study in patients with accessible tumors for exploratory biomarker analysis, including evaluation of LIV-1 expression. In patients with inaccessible tumors or other safety concerns, archival tissue may be submitted if it was collected after completion of the patient's most recent cytotoxic therapy. If neither is available, please discuss with medical monitor. In Part D only, PD-L1 CPS <10 status will be determined locally at the investigative site by a PD-L1 immunohistochemistry (IHC) assay using the 22C3 clone. Patients must have at least 1 tumor lesion ≥10 mm in the longest diameter or lymph node of ≥15 mm in the short axis as measured by RECIST v 1.1. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate renal, hepatic, and hematological function are required at baseline. Patients must not have received prior immuno-

oncology therapy, including checkpoint inhibitors (CPIs), and can have no history of other serious malignancy within the past 3 years. Pre-existing neuropathy ≥ Grade 2 is not permitted.

Number of Planned Patients

Approximately 189–211 patients are expected to be enrolled, including approximately 12–24 patients enrolled in Part A (LV dose de-escalation), approximately 73 patients in Part B (expansion), approximately 64 patients in Part C (LV weekly [q1wk] dosing), and approximately 40 patients in Part D (LV Day 1, Day 8 in 21-day cycle dosing). In Part B, approximately 48 patients will be enrolled at the maximum administered dose (MAD) of LV 2.5 mg/kg and approximately 25 patients will be enrolled at the lower dose of 2.0 mg/kg LV in combination with pembrolizumab. In Part C, approximately 64 patients, including approximately 60 patients in the expansion cohort, will be enrolled and will receive LV 1.0 or 1.25 mg/kg on Day 1, Day 8, and Day 15 in every 21-day cycle, in combination with pembrolizumab administered on Day 1 of every cycle. In Part D, approximately 40 patients will be enrolled and will receive LV 1.5 mg/kg on Day 1 and Day 8 (**off** Day 15) in every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle.

Study Design

This is a single-arm, open-label, multicenter trial designed to assess the safety and efficacy of LV in combination with pembrolizumab for the treatment of LA/M TNBC. Patients will be enrolled into Part A, Part B, Part C, and Part D sequentially. Patients will enroll in Part B Cohort 1 and Part B Cohort 2 sequentially.

In Part A, patients will receive a dose of LV 2.5 mg/kg as an intravenous (IV) infusion over approximately 30 minutes followed by pembrolizumab 200 mg IV over approximately 30 minutes on Day 1 of each 21-day cycle. In consultation with the sponsor, eligible patients already on treatment prior to Amendment 2, may have their maximum weight cap per infusion increased to 100 kg or remain at 80 kg, if they are receiving benefit (complete response [CR], partial response [PR], or stable disease [SD]). Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF). Dosing may be de-escalated based upon the frequency of dose- limiting- toxicities (DLTs) in Cycle 1.

Part B includes 2 expansion cohorts. Part B Cohort 1 will receive the MAD of LV 2.5 mg/kg. Part B Cohort 2 will receive the dose of LV 2.0 mg/kg. Patients will enroll sequentially into Cohort 1 followed by Cohort 2. Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF).

In Part C, patients will receive LV 1.0 or 1.25 mg/kg on Day 1, Day 8, and Day 15 in every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle. Part C will have dose escalation and expansion cohorts. Dose escalation in Part C will be conducted using the modified toxicity probability interval (mTPI) method (Ji 2010). At least 2 patients will be enrolled in each dose escalation cohort. The safety monitoring committee (SMC) will evaluate the safety of each dose-level cohort and make dose escalation/de-escalation recommendations using the mTPI decision rules. Only 1 dose-escalation cohort will be open at a time.

The dose-expansion cohorts in Part C will assess the efficacy, safety, and tolerability in a larger number of patients. Dose-expansion cohorts may be opened at any dose level that has cleared DLT evaluation. DLT evaluation will only include data from the dose-escalation cohorts; however, the totality of data from all patients at each dose level will be used to determine the recommended q1wk LV dose.

In Part D, patients will receive LV 1.5 mg/kg administered on Day 1 and Day 8 (**off** Day 15) of every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle. Ongoing, real-time, continuous review of patient safety and serious adverse events (SAEs) will be conducted by the sponsor's Drug Safety Department. Additionally, the independent safety monitoring committee (ISMC) will ensure periodic safety data review throughout the study.

Under Amendment 2 and later, dosing for patients in Parts A and B is based on patient actual body weight, except for patients weighing >100 kg, where dosing will be based on a 100 kg maximum weight per infusion. For patients in Parts C and D, LV dosing is based on the patient's actual body weight but there will be no weight cap per infusion. An individual's dose may be modified based upon treatment-related adverse events (AEs). In all patients,

pembrolizumab 200 mg will be administered by IV infusion approximately 60–90 minutes after administration of LV.

Responses will be assessed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI) scan every 6 weeks (±3 days) for the first 12 months after the first dose of LV and pembrolizumab and every 12 weeks (±7 days) thereafter through the end of the safety follow-up period. No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. Objective responses will be confirmed at least 4 weeks after first documentation of response. RECIST v1.1 will be used to score responses for the primary and secondary endpoints, and iRECIST will be used for exploratory endpoints. Investigators will make treatment decisions based on site assessments of scans using iRECIST.

Patients will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, or study termination by the sponsor. Pembrolizumab may be administered for a maximum of 35 cycles (approximately 2 years). If LV or pembrolizumab is discontinued, patients may continue to receive the other drug with medical monitor approval. Patients who discontinue study treatment in the absence of disease progression will be followed every 6 weeks for response assessments, physical examinations, and survival until withdrawal of consent, initiation of a new anticancer therapy, death, or study closure, whichever occurs first. After 1 year on study, the frequency of follow-up visits will be reduced to every 12 weeks. All patients, including those with progressive disease (PD), will be followed for survival until the end of the safety follow-up period, death, or study closure, whichever occurs first.

After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted every 12 weeks (±2 weeks) starting from the last radiographic scan demonstrating disease progression or from initiation of the new anticancer treatment. Survival follow-up will continue until the end of the safety follow-up period, death, or study closure, whichever comes first. Follow-up may be conducted with clinic visits or telephone calls. No further response assessments are required.On a periodic basis, an SMC will monitor the safety of patients participating in the trial. The SMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. An ongoing, real-time review of patient safety and (SAEs) will also be conducted by the sponsor's Drug Safety Department. In addition, an ISMC composed of physicians who are not involved in this study, as well as sponsor representatives, will periodically review cumulative safety data and provide recommendations to the sponsor. Continuous monitoring of the benefit-risk profile will be conducted and continuation of enrollment to the cohort may be altered depending on the benefit-risk profile.

Test Product, Dose, and Mode of Administration

Parts A and B: LV (every 3 weeks [q3wk]); 2.0 or 2.5 mg/kg; approximately 30-minute IV infusion on Day 1 of every 21-day cycle.

Part C: LV (q1wk); 1.0 or 1.25 mg/kg; approximately 30-minute IV infusion on Day 1, Day 8, and Day 15 of every 21-day cycle. The maximum dose will be 200 mg per infusion.

Prior to Amendment 2, the weight cap is 80 kg. For patients in Parts A and B treated under Amendment 2 and later, the maximum weight cap per infusion will be increased from 80 kg to 100 kg. Patients who receive >200 mg LV per infusion in Parts A and B are also required to be administered prophylactic G-CSF.

Part D: LV 1.5 mg/kg; approximately 30-minute IV infusion on Day 1 and Day 8 (**off** Day 15) of every 21-day cycle. The maximum dose will be 200 mg per infusion.

Pembrolizumab: 200 mg; 30-minute IV infusion every 21 days given approximately 60–90 minutes after LV.

Duration of Treatment

Patients may continue on treatment until disease progression as determined by iRECIST, unacceptable toxicity, investigator decision, consent withdrawal or study termination by the sponsor. Pembrolizumab may be administered for a maximum of 35 cycles (approximately 2 years).

Efficacy Assessments

Antitumor activity will be assessed by radiographic tumor imaging at protocol-specified time points. Response assessment for primary and secondary efficacy endpoints will be evaluated using RECIST v1.1. Exploratory efficacy endpoints will be evaluated using iRECIST.

Pharmacokinetic and Immunogenicity Assessments

Patient serum and plasma samples will be obtained for LV PK and ATA evaluation at protocol specified time points. Concentrations of antibody-drug conjugate (ADC) LV and monomethyl auristatin E (MMAE) will be measured in plasma and ATA in serum.

Starting with Amendment 11, PK and immunogenicity assessments will not be conducted after Cycle 1.

Biomarker Assessments

Tumor samples and blood will be collected at protocol-specified time points. Biomarker analysis will not be utilized for patient selection (with the exception of PD-L1 for Part D patients). Biomarker assessments in tumor tissue may include, but are not limited to: measurement of LIV1 and PD-L1 proteins, gene expression, disease subtype, tumor immune microenvironment, and mutational load. Assessments in blood may include but are not limited to: cytokine or other protein measurements, abundance and phenotypes of immune cell subsets, and circulating nucleic acids. Methods of analysis may include IHC, multiplex immune histofluorescence (mIHF), mutation and gene expression profiling by Next Generation Sequencing, flow cytometry, ELISA, and T cell receptor beta (TCRβ) immunoSEQ analysis.

Starting with Amendment 11, biomarker assessments will not be conducted after Cycle 1.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, physical examination findings, vital signs, electrocardiograms (ECGs), concomitant medications, and laboratory tests.

Statistical Methods

Safety and efficacy endpoints will be summarized with descriptive statistics.

The safety analysis set will include patients treated with any amount of LV or pembrolizumab. This is also referred to as the all treated patients set for some efficacy analyses. The DLT-evaluable (DE) analysis set includes all patients in the safety analysis set who either (1) experience a DLT or (2) receive at least 75% of intended LV and pembrolizumab doses and are followed for the full DLT evaluation period (Cycle 1). The DE patient set will be the primary population for Part A, and will be used for the determination of the MAD for Part B. The all treated analysis set includes all enrolled patients who receive any amount of LV or pembrolizumab and will be the primary set for efficacy analysis. The efficacy-evaluable (EE) set includes all patients in the all treated analysis set who have both a baseline and at least 1 evaluable post-baseline disease assessment according to the RECIST v1.1 and iRECIST criteria, or per investigator determination of clinical disease progression.

Exact 95% confidence intervals (CIs) for ORR and DCR will be provided. DOR, PFS, and OS will be analyzed using the Kaplan-Meier method. The primary analyses of efficacy endpoints will be performed for all treated patients analysis set. All safety analyses will be based on the safety analysis set.

Approximately 60 patients total are expected to be enrolled at the MAD assuming that Part A will enroll 12 patients at the MAD and Part B Cohort 1 will enroll approximately 48 patients, at the MAD. Based on the SGNLVA-001 Phase 1 study, it is estimated that about 70% of patients are LIV-1-positive. Thus, approximately 42 LIV-1-positive patients in total will be enrolled at the MAD. Assuming the observed ORR is between 50% and 70%, the widths of 2-sided 95% CIs are summarized below.

Confirmed ORR	Expected width of 95% CI on LIV-1-positive patients (N=42)	Expected width of 95% CI on all patients at the MAD (N=60)
50%	±16%	±13%
60%	±16%	±13%
70%	±15%	±12%

Part B Cohort 2 will enroll approximately 25 patients at 2.0 mg/kg. With the patients in Part A enrolled at 2.0 mg/kg, approximately 30 patients in total will be enrolled at 2.0 mg/kg. Assuming the observed ORR is between 50-70%, the widths of 2-sided 95% CIs are summarized as below.

Confirmed ORR	Expected width of 95% CI on all patients at 2.0 mg/kg (N=30)
50%	±18%
60%	±18%
70%	±16%

Part C will enroll approximately 64 patients in total and 62 patients at selected dose level (assuming 2 patients in each dose escalation cohort of 1.0 and 1.25 mg/kg, and 60 patients in the expansion cohort at 1.25 mg/kg). Assuming the observed ORR is between 50%–70%, the table below summarizes the 2-sided 95% exact CIs among the 62 patients at the selected dose level of 1.25 mg/kg (2 in dose escalation and 60 in dose expansion cohort).

Number of confirmed Objective Responses	Confirmed ORR (%)	95% exact CI (N=62)
31	50%	37%, 63%
37	60%	46%, 72%
43	69%	56%, 80%

Approximately 40 patients will be enrolled in Part D. Ongoing, real-time, continuous review of patient safety and SAEs will be conducted by the sponsor's Drug Safety Department. Additionally, the ISMC will ensure periodic safety data review throughout the study.

Presented in the table below are the 2-sided 95% exact CIs among 40 patients at 1.5 mg/kg assuming the observed ORR is between 50% and 70%.

Number of confirmed Objective Responses	Confirmed ORR (%)	95% exact CI (N=40)
20	50%	34%, 66%
24	60%	43%, 75%
28	70%	53%, 83%

This sample size of 40 patients would additionally provide the following probabilities of observing at least 1 patient having an AE, as summarized below.

True AE Incidence Rate	Probability of Observing at Least One Patient Having an AE (N=40)
5%	87%
10%	99%

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ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BICR	blinded independent central review
β-hCG	beta human chorionic gonadotropin
BC	breast cancer
CEA	carcinoembryonic antigen
CBC	complete blood count
CBR	clinical benefit rate
cfDNA	cell-free DNA
CI	confidence interval
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DE	DLT-evaluable
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EE	efficacy-evaluable
EOT	end of treatment
ER	estrogen receptor
FFPE	formalin fixed paraffin embedded
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate

GM-CSF	granulocyte macrophage colony-stimulating factor
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HER2	human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
IB	Investigator's Brochure
ICD	immunogenic cell death
ICH	International Council for Harmonisation
iCPD	confirmed progressive disease
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
irAE	immune-related adverse events
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
ISMC	independent safety monitoring committee
iUPD	unconfirmed progressive disease
IV	intravenous
LA/M	locally-advanced or metastatic
LAR	legally authorized representative
LV	ladiratuzumab vedotin; SGN-LIV1A
mAb	monoclonal antibody
MAD	maximum administered dose
mBC	metastatic breast cancer
mTNBC	metastatic triple-negative breast cancer
mTPI	modified toxicity probability interval
MedDRA	Medical Dictionary for Regulatory Activities
mIHF	multiplex immune histofluorescence
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based PK
PCR	polymerase chain reaction
PD	progressive disease

PD-1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PPoS	Bayesian predictive probability of success
PR	partial response
PR	progesterone receptor
PT	prothrombin time
PTT	partial thromboplastin time
q1wk	every 1 week/weekly
q2wk	every 2 weeks
q3wk	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	safety monitoring committee
SUSARs	suspected unexpected serious adverse reactions
TCRβ	T cell receptor beta
TIL	tumor-infiltrating lymphocyte
TN	triple-negative
TNBC	triple-negative breast cancer
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USP	United States Pharmacopeia
WBC	white blood cell

1. INTRODUCTION

1.1. Breast Cancer

Apart from cancers of the skin, breast cancer (BC) is the most common malignancy in women in the US. Despite recent advances in treatment, it is second only to lung cancer as a cause of cancer death in women. In 2017, it was estimated that there would be 252,710 new cases of invasive BC in women in the US, and approximately 40,610 deaths (American Cancer Society (ACS) 2017). For the vast majority of patients, the etiology is unknown. While the disease can arise from either the lobular or ductal epithelium, 85%–90% of invasive carcinomas are ductal in origin (Dupont 1985). BC is a heterogeneous disease and treatment is based on a number of prognostic and predictive factors that include tumor histology, hormone receptor content and human epidermal growth factor receptor 2 (HER2) status, as well as axillary nodal involvement, detectable metastatic disease, patient age, and menopausal status. Treatment varies from local control with surgery and/or radiation therapy to systemic disease requiring cytotoxic chemotherapy, endocrine therapy, biologic agents, or a combination of these. Most new diagnoses of BC are made at an early stage; however, approximately 1/3 of these patients will eventually develop recurrent or metastatic disease (O'Shaughnessy 2005). Localized disease is curable, with a 5-year relative survival of 98% that decreases to 84% in those whose disease has spread to the regional lymph nodes. The prognosis is poor in those with metastatic breast cancer (mBC), with a 5-year relative survival of less than 24% (Howlader 2013). Hence, the current therapies for metastatic disease delay disease progression, but are not curative.

Metastatic BC remains an incurable illness for the majority of patients. Only a select few with highly chemosensitive tumors will achieve a complete response (CR) with combination chemotherapy regimens (Greenberg 1996). Hence for the remaining patients, treatment is palliative and is initiated in an attempt to delay disease progression, alleviate disease symptoms, improve or maintain quality of life, and potentially prolong survival (O'Shaughnessy 2005). Women with metastatic disease are initially stratified according to tumor hormone receptor status and HER2 amplification. A variety of treatment options are available, including endocrine therapy such as tamoxifen, aromatase inhibitors, fulvestrant for women with hormone receptor-positive disease, or cytotoxic chemotherapy administered as monotherapy or in combination with other cytotoxic drugs or biologics (e.g., trastuzumab for HER2-positive tumors). Current guidelines recommend systemic chemotherapy for women with hormone-receptor negative disease that is not localized to bone or soft tissue and is associated with symptomatic visceral disease or for women with hormone receptor-positive disease that has demonstrated resistance to endocrine therapy (Carlson 2011).

Resistance to chemotherapy accounts for greater than 90% of the treatment failures in patients with metastatic cancer (Longley 2005; Rivera 2010). As a result, treatment options are limited for patients with mBC who have had prior exposure to chemotherapy. Once patients progress to requiring chemotherapy in the metastatic setting, 25%–45% of them achieve an objective response with first line single-agent chemotherapy for metastatic disease and have a time to progression (TTP) of 5–8 months (Burstein 2011). With second line chemotherapy in the metastatic setting, the objective response rate (ORR) diminishes to 15%–30% with a TTP of 2–5

months, and following third line therapy, the ORR is 0%–20% with a TTP of 1–4 months. Hence, for women with mBC who require chemotherapy, the clinical benefits are marginal, and none are curative.

1.2. Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) accounts for approximately 10%–20% of BCs. These tumors lack estrogen, progesterone, and HER2 receptors and are associated with poorer prognosis compared to other types of BC. TNBC has a high proliferative rate and a heterogeneous gene expression profile. Patients with metastatic triple-negative breast cancer (mTNBC) have a median overall survival (OS) of less than 1 year (Rodler 2010; den Brok 2017).

The lack of hormone and HER2 receptors limits treatment options in TNBC to currently available chemotherapy in both the local and metastatic settings. Considerations for treating locally-advanced or metastatic (LA/M) disease include previous chemotherapy exposure, performance status, comorbid conditions, tumor characteristics, patient preference, and quality of life concerns. Sequential single-agent systemic chemotherapies associated with minimal toxicity are preferred. Commonly used single agents include taxanes and anthracyclines. Standard clinical practice is to continue first line chemotherapy until progression. The choice of chemotherapy for mBC is not well defined. There are no published evidence-based clinical guidelines with explicit recommendations about what systemic treatment is more appropriate for these patients with advanced TNBC. In recent Phase 2 and 3 TNBC trials on first line single-agent chemotherapies, including taxanes, platinums, and anthracyclines, the ORR was approximately 29%–40% and the median progression-free survival (PFS) was 3–6 months (Helwick 2015; Isakoff 2015; Rugo 2015). Combination therapies of traditional chemotherapeutic agents (e.g., gemcitabine + carboplatin) are also used. Recent analyses show combination therapies confer little to no survival benefits and have a higher toxicity profile when compared to the sequential single-agent chemotherapy (Carlson 2011; Dear 2013).

Given the current landscape, there is an obvious and urgent need for novel therapies in the first line LA/M setting that can provide clinical and survival benefit.

1.3. LIV-1

LIV-1 is a member of the solute carrier family 39, and is a multispan transmembrane protein with putative zinc transporter and metalloproteinase activity (Taylor 2003). It was first identified as an estrogen induced gene in the BC cell line ZR-75-1 (Manning 1988). Subsequently, normal tissue expression has been demonstrated in hormonally-regulated tissues with the highest expression in breast and prostate samples (Sussman 2014).

LIV-1 expression has been linked with malignant progression to metastasis and is associated with lymph node involvement in BC (Manning 1994). It is expressed in almost all mBC tumors, with moderate-to-high expression in 86% of HR+/HER2-, 74% of HER2+, and 71% of TNBCs (Forero 2016). LIV-1 has been detected in a number of cancer types including breast, prostate, melanoma, ovarian, cervical, uterine, and pancreatic cancer (Manning 1988; Manning 1994; Dressman 2001; Tozlu 2006; Unno 2009; Sussman 2014). In an immunohistochemistry (IHC) analysis conducted by Seagen Inc., the highest prevalence and level of expression is seen in

breast ductal carcinoma (93% of relapsed post-treatment patient samples), prostate adenocarcinoma (72% of relapsed post-treatment, castration-resistant patient samples) and melanoma (82% of primary melanoma biopsies) (Sussman 2014).

1.4. Ladiratuzumab Vedotin

Ladiratuzumab vedotin (LV; SGN-LIV1A) is an antibody-drug conjugate (ADC) directed against the LIV-1 antigen and is being developed to treat patients with LIV-1-positive malignancies, such as BC. The antibody backbone of LV, hLIV22, is a humanized IgG1 monoclonal antibody (mAb) that is chemically conjugated to a synthetic analog (monomethyl auristatin E [MMAE]) of the naturally occurring tubulin-disrupting drug, dolastatin 10. The protease-cleavable valine-citrulline maleimidocaproyl linker covalently attaches MMAE to hLIV22. An average of 4 MMAE molecules is present on each antibody molecule.

1.4.1. Mechanism of Action of LV

Subsequent to binding to cell-surface LIV-1, LV is internalized and trafficked through the endocytic pathway to reach the lysosomes. Proteolytic degradation of the drug linker in lysosomes releases MMAE, which becomes available for tubulin binding. Interaction between MMAE and tubulin disrupts the cellular microtubule network, arrests cells at the G2/M phase of the cell cycle, prevents cell division, and eventually leads to cellular apoptosis. Antitumor activity and immunospecificity of LV have been demonstrated in vitro and in vivo with models representing LIV-1-expressing breast, prostate, and cervical cancer.

1.4.2. Preclinical Experience with LV

The toxicity of LV following intravenous (IV) administration has been evaluated in rats (single- and repeat-dose studies) and monkeys (single-dose study only). The dose-limiting toxicity (DLT) was bone marrow suppression, with concomitant reductions in hematology endpoints (predominantly anemia and neutropenia). Dose-dependent toxicities included liver, small intestine, mammary glands, thymus, kidney, spleen, ovary, mesenteric lymph node, skin, and rectum.

Similar hematopoietic cell depletion and target organs of toxicity have been observed for MMAE (the cytotoxic component of LV) administered at molar equivalents of ADC highest non-severely toxic dose levels. An additional MMAE-related toxicity, not observed to date in the LV studies, is degeneration of spermatic epithelium in the male reproductive tract. Treatment with MMAE during pregnancy in rats also led to embryo-fetal development toxicity characterized by significant increases in total resorptions, post implantation loss, early delivery, and loss of viable fetuses.

A complete summary of the nonclinical data relevant to the investigational product and its study in human subjects is provided in the LV Investigator's Brochure (IB).

1.4.3. Clinical Experience with LV

The safety and efficacy of LV is being evaluated in an ongoing phase 1 dose-escalation study in patients with heavily pretreated, unresectable LA/M TNBC (Protocol SGNLVA-001). In the 53 patients treated to date with monotherapy LV, including 35 patients with triple-negative (TN)

disease, the maximum tolerated dose (MTD) was not exceeded after escalating to 2.8 mg/kg every 3 weeks (q3wk). No DLTs in Cycle 1 were observed in the 19 DLT-evaluable (DE) patients. LV was generally well tolerated, and the most common adverse events (AEs) of any grade included fatigue, nausea, alopecia, decreased appetite, constipation, peripheral neuropathy, and neutropenia. Of the 30 patients with LIV-1 positive TN disease evaluable for response treated at doses from 1.5–2.8 mg/kg, 11 (37%) achieved an objective partial response (PR) (no complete remissions) including 6 (20%) that were confirmed PR (as presented by Forero A, et al at SABCS 2016). Disease control rate (DCR) was 67% (11 PR, 9 stable disease [SD]) and clinical benefit rate (CBR=OR + SD ≥24 weeks) was 47% (14 patients). Given the activity observed with LV in patients with heavily pretreated LA/M TNBC, there is reason to support the hypothesis that LV will have significant single-agent activity in patients with previously untreated LA/M TNBC.

See the LV IB for complete clinical safety information.

1.5. Pembrolizumab Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the IB/approved labeling for detailed background information on MK-3475.

1.5.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley 2005; Hunder 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Okazaki 2001; Greenwald 2005).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-Variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T cell signaling cascade (Okazaki 2001; Chemnitz 2004; Sheppard 2004; Riley 2009). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry 2005; Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in unresectable LA/M TNBC.

1.5.2. Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome 2003; Blank 2004; Hirano 2005; Curran 2010; Pilon-Thomas 2010; Weber 2010; Spranger 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma (Strome 2003; Zhang 2004; Nomi 2007; Curran 2010; Pilon-Thomas 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

Justification for the planned dose of pembrolizumab for this study is detailed in Section 3.2.3.1.

1.6. Rationale for Study

For patients with mBC, there are no curative options. While systemic treatments aim to prolong survival, control disease progression, alleviate symptoms, and enhance patient quality of life, the 5-year survival rates for patients with distant-stage disease remain low at 24% (Howlader 2013). Evidence of anti-tumor activity has been observed with LV monotherapy in patients with heavily pretreated TNBC, and it is therefore warranted to explore combining this targeted agent with other treatments, such as checkpoint inhibitors (CPIs).

Although CPIs represent a significant advancement in the treatment of cancer, patients with LA/M TNBC continue to have a very poor prognosis and combining CPIs with a novel therapy, such as LV, may be beneficial. Anti-PD(L)1 agents in combination with chemotherapy have been shown to be efficacious in mTNBC (Schmid 2018). LV and pembrolizumab act through

distinct and complementary mechanisms of action. LV, a directly cytotoxic agent, may induce immunogenic cell death (ICD). By administrating LV in combination with pembrolizumab, it is hypothesized that LIV-expressing tumor cells killed by LV will potentially activate the innate immune system to initiate antitumor immune response. At the same time, the CPI pembrolizumab unleashes the antitumor activity of T lymphocytes by targeting the T cell inhibition pathway. There are currently no data available for this combination in BC; however, brentuximab vedotin, another ADC with the same MMAE drug linker, has been studied in combination with the CPI nivolumab for treatment of Hodgkin lymphoma (HL). Preliminary data suggest that brentuximab vedotin, a CD30-directed ADC, increases tumor immunogenicity by induction of ICD, antigen presentation, and tumor immune infiltration (Gardai 2015). Preliminary clinical data for brentuximab vedotin in combination with nivolumab in relapsed/refractory HL demonstrate increased antitumor activity above what would be expected with the additive effects of each agent, although the number of patients treated is small (n=12) (Diefenbach 2017).

It is hypothesized that combining LV with pembrolizumab will result in improved response rates and may be synergistic, with the potential to prolong PFS and OS in patients with LA/M BC. Moreover, both agents are well tolerated, have few overlapping Grade 3–5 toxicities, and can be infused in the outpatient setting. This study will evaluate the safety and antitumor activity of LV in combination with pembrolizumab in a population of patients for whom standard therapy is unsatisfactory.

A complete summary of the clinical and nonclinical data relevant to LV and pembrolizumab and their study in human subjects is provided in each product's IB. The sponsor acknowledges that no preclinical data to characterize the antitumor activity and toxicity of the LV and pembrolizumab combination have been generated.

2. OBJECTIVES AND ENDPOINTS

Primary Safety Objectives	Corresponding Endpoint
Evaluate the safety and tolerability of the combination of LV and pembrolizumab in patients with LA/M TNBC	Type, incidence, severity, seriousness, and relatedness of AEs Laboratory abnormalities
Identify the recommended dose and schedule of LV in combination with pembrolizumab in patients with LA/M TNBC	Incidence of DLT
Primary Efficacy Objective	**Corresponding Endpoint**
Evaluate the confirmed ORR of the combination of LV and pembrolizumab in patients with LA/M TNBC	Confirmed ORR as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary Efficacy Objectives	**Corresponding Endpoints**
Evaluate the DOR, DCR, PFS, and OS	DOR as determined by RECIST v1.1 DCR as determined by RECIST v1.1. PFS as determined by RECIST v1.1 OS
Exploratory Efficacy Objectives	**Corresponding Endpoints**
Evaluate the ORR, DOR, DCR, and PFS according to iRECIST	ORR as determined by iRECIST DOR as determined by iRECIST DCR as determined by iRECIST PFS as determined by iRECIST
Pharmacokinetic and Immunogenicity Objectives	**Corresponding Endpoints**
Assess pharmacokinetics (PK) and incidence of antitherapeutic antibodies (ATAs) of LV	Selected PK parameters for LV, and MMAE Incidence of ATAs to LV
Biomarkers Objectives	**Corresponding Endpoints**
Evaluate the PD-L1 and LIV-1 expression-response relationship	PD-L1 and LIV-1 expression-response relationship following treatment with LV and pembrolizumab
Assess exploratory biomarkers (e.g., in the tumor immune microenvironment or periphery) of study treatment-mediated pharmacodynamic effects	Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with LV/pembrolizumab (see Section 7.4)

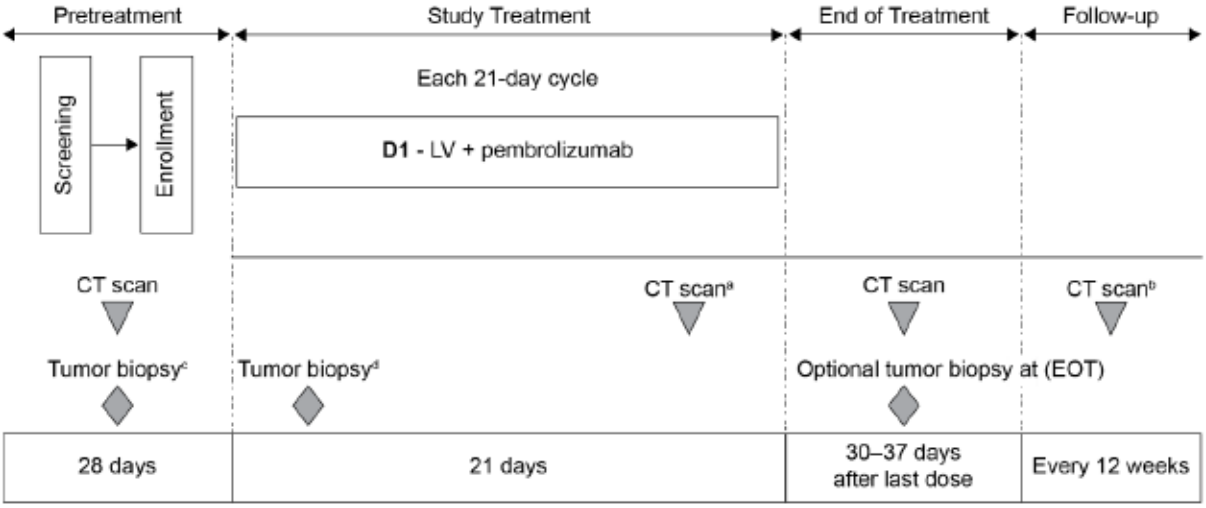
RECIST=Response Evaluation Criteria in Solid Tumors; iRECIST=Immune Response Evaluation Criteria in Solid Tumors.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

The study consists of Parts A, B, C, and D. Parts A and B are depicted schematically in Figure 1. The study assessment schedule will be the same for Parts A and B, with exceptions to Cycle 1 Day 3 and Day 5 (see Appendix B). Parts C and D are depicted in Figure 2. The study assessment schedule will be the same for Parts C and D, with the exception of Day 15 dosing only relevant to Part C (see Appendix C).

Figure 1: SGNLVA-002 study schema (Parts A and B)



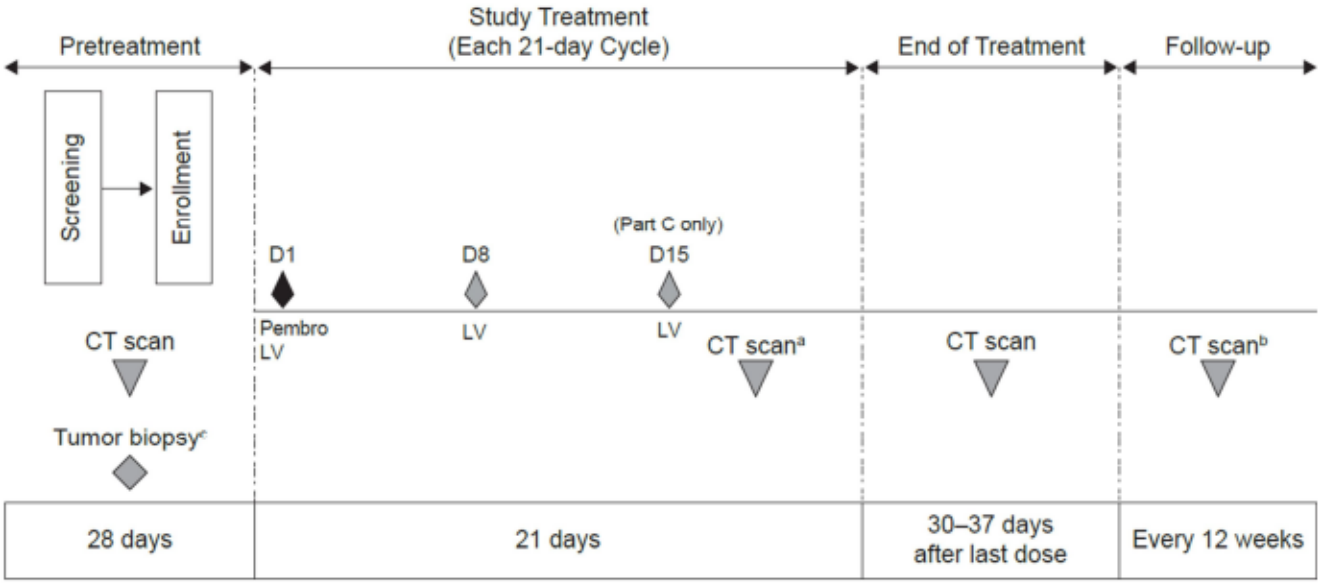
a Response assessments to be performed every 6 weeks (±3 days) for the first 12 months and every 12 weeks (±7 days) thereafter, regardless of dose delays. Following end of study treatment, no additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. For first objective response (CR or PR), a scan will be performed at least 4 weeks after first documentation of response.

b Patients who discontinue study treatment in the absence of disease progression will continue to be evaluated for response every 6 weeks until completion of the safety follow-up period (30 days post treatment for LV and 90 days post treatment for pembrolizumab). The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.5.1.2 and Section 7.5.1.4 for patients who are still receiving treatment or in the safety follow-up period. See Section 0 for details.

c Newly obtained core or excisional tumor biopsy. For patients with inaccessible tumors or other safety concerns, archival tissue may be submitted. If neither adequate fresh nor archived tissue is available, please contact the medical monitor. See Section 7.4.1 for details.

d Biopsy obtained on Cycle 1 Day 5 (window Days 4–7) for patients in Part A with accessible tumors or at Cycle 1 Day 15 (window Days 15–21) for patients in Part B with accessible tumors.

Figure 2: SGNLVA-002 study schema (Parts C and D)



a Response assessments to be performed every 6 weeks (±3 days) for the first 12 months and every 12 weeks (±7 days) thereafter, regardless of dose delays. For first objective response (CR or PR), a scan will be performed at least 4 weeks after first documentation of response. Following end of study treatment, no additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time.

b Patients who discontinue study treatment in the absence of disease progression will continue to be evaluated for response every 6 weeks until completion of the safety follow-up period (30 days post treatment for LV and 90 days post treatment for pembrolizumab). The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.5.1.2 and Section 7.5.1.4 for patients who are still receiving treatment or in the safety follow-up period. See Section 0 for details.

c Archival or newly obtained core or excisional tumor biopsy. If neither archived tissue nor adequate fresh is available, please contact the medical monitor. See Section 7.4.1 for details.

Patients will be evaluated for response assessments every 6 weeks (±3 days) for the first 12 months, and every 12 weeks (±7 days) thereafter, regardless of dose delays, thereafter through the end of the safety follow-up period. No additional scans or response assessments are required after the safety follow-up period. Additional scans or response assessments may be performed as part of the patient's standard of care at any time. Patients who achieve SD or better will be eligible to continue receiving study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, or study termination by the sponsor. Intrapatient dose escalation or de-escalation to a dose level shown to be safe may be permitted with sponsor approval in the event that a patient tolerates study treatment.

Pembrolizumab administration will be capped at 35 cycles (approximately 2 years).

Disease progression for determining eligibility of treatment continuation will be based on immune Response Evaluation Criteria for Solid Tumors (iRECIST).

3.1.1. Part A: Dose De-escalation

This part of the study is designed to evaluate the safety of LV administered in combination with pembrolizumab, and to identify the maximum administered dose (MAD) for Part B. Patients will receive LV 2.5 mg/kg IV (maximum weight cap per infusion at 80 kg) as a 30-minute infusion

followed by pembrolizumab 200 mg IV as a 30-minute infusion on Day 1 q3wk. Patients treated under Amendment 2 and later will receive LV 2.5 mg/kg (capped at 100 kg). In consultation with the sponsor, eligible patients already on treatment prior to Amendment 2, may have their maximum weight cap per infusion increased to 100 kg or remain at 80 kg, if they are receiving benefit (CR, PR, or SD). Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF). Pembrolizumab will be administered approximately 60 to 90 minutes after infusion of LV is complete. DLTs will be assessed in the first treatment cycle, through Cycle 2 Day 1.

Blood samples for PK and immunogenicity analysis may be collected to support the study endpoints. Pharmacodynamic and exploratory biomarker studies will also be conducted on patient blood samples and tumor tissue obtained throughout the trial, including samples obtained to determine eligibility. As of protocol Amendment 11, no PK, immunogenicity, PD, or biomarker samples will be obtained after Cycle 1.

Part A of this study will enroll approximately 12–24 patients. The dose de-escalation plan for LV in this part of the study requires de-escalation in the event that the DLT rate is ≥1/3 of patients given the current dose. This plan is as follows:

Initially, 6 patients will be given the starting dose of 2.5 mg/kg (capped at 80 kg prior to Amendment 2 or 100 kg under Amendment 2 and later). Enrollment will proceed as follows:

a. If <2 of 6 patients experience DLT at 2.5 mg/kg, 6 more patients will be enrolled at the same dose level of 2.5 mg/kg.
    i. If <4 of these 12 patients experience DLTs, Part B will be initiated at 2.5 mg/kg.
    ii. If ≥4 of 12 patients experience DLTs, the dose will be de-escalated to 2.0 mg/kg and the study will proceed as described for dose de-escalation below.
b. If ≥2 of 6 patients experience DLT at 2.5 mg/kg, the dose level will be lowered to 2.0 mg/kg (capped at 80 kg prior to Amendment 2 or 100 kg under Amendment 2 and later) and 6 patients will be enrolled at this dose level.
    i. If <2 of 6 patients given 2.0 mg/kg experience DLTs, 6 more patients will be enrolled at 2.0 mg/kg.
        - If <4 of these 12 patients experience DLTs. Part B will initiate at 2.0 mg/kg.
        - If ≥4 of 12 patients experience DLTs, the dose of LV will be further de-escalated as determined by the sponsor in consultation with the safety monitoring committee (SMC).
    ii. If ≥2 of 6 patients given 2.0 mg/kg experience DLTs, the dose of LV will be further de-escalated as determined by the sponsor in consultation with the SMC.

An SMC consisting of the medical monitor, the study statistician, a drug safety representative, and study investigator(s) will monitor patient safety throughout the trial. In Part A, the safety of

combination treatment will be evaluated by the SMC prior to expansion of enrollment in Part B. After 6 patients have been followed through the end of the DLT period, or at the point that 2 or more patients experience a DLT, whichever comes first, the SMC will review all available data and make a recommendation for one of the following:

1. To explore Part A further and treat up to 6 additional patients at the same dose level previously tested, or with any modifications that may include, but are not limited to:
   a. Dose de-escalation of LV to 2.0 mg/kg
   b. Evaluation of an intermediate or lower dose level of LV
   c. Dose re-escalation back to LV 2.5 mg/kg (capped at 100 kg) if 2.0 mg/kg is proven to be safe
2. To close the study to additional enrollment

In addition to the SMC, an independent safety monitoring committee (ISMC) composed of physicians who are not involved, as well as sponsor representatives, in this study will periodically review cumulative safety data and provide recommendations to the sponsor.

3.1.2. Part B: Expansion

Part B is designed to further evaluate the safety and antitumor activity of the combination of LV and pembrolizumab and to maximize the benefit-risk profile. This part of the study will be conducted in 2 cohorts. Patients will enroll sequentially into Cohort 1 followed by Cohort 2. Part B Cohort 1 will receive the MAD of LV 2.5 mg/kg, (capped at 100 kg) in combination with pembrolizumab. Part B Cohort 2 will receive a dose of LV 2.0 mg/kg (capped at 100 kg), in combination with pembrolizumab (see Section 3.2.3.1 for rationale of Part B Cohort 2). Patients receiving >200 mg LV per infusion are required to be administered prophylactic granulocyte-colony stimulating factor (G-CSF).

Patients will receive LV and pembrolizumab q3wk. Pembrolizumab, 200 mg IV will be given per the US prescribing information on the same day as LV, approximately 60-90 minutes following LV infusion.

Approximately 73 patients will be enrolled in Part B of the study (approximately 48 in Cohort 1 and approximately 25 in Cohort 2).

The SMC and ISMC will continue to monitor the safety of LV and pembrolizumab. The SMC will meet regularly during Part A but convene as needed in Part B. The ISMC will meet periodically.

3.1.3. Part C: Weekly LV dosing

Part C will test weekly (q1wk) dosing of LV administered on Day 1, Day 8, and Day 15 of every 21-day cycle not to exceed 200 mg per infusion in combination with pembrolizumab administered on Day 1 of every cycle.

Part C will consist of

1. Dose escalation cohorts
2. Expansion cohorts

Up to approximately 64 patients may be enrolled in Part C. The totality of data from all patients in dose escalation and expansion cohorts will be used to determine the recommended q1wk LV dose in combination with pembrolizumab.

Dose escalation will begin at dose level 0. The first 2 patients enrolled at each dose level will be evaluated for DLTs. If LV dose level 0 clears DLT evaluation, subsequent patients may be enrolled at dose level 1 or in the dose level 0 expansion cohorts. See Table 2 for dose levels and Section 3.2.1 for details on assigning patients to treatment groups.

3.1.3.1. Part C: Dose Escalation Cohort

The starting dose of LV will be dose level 0 at 1.0 mg/kg on Day 1, Day 8, and Day 15. Planned dose levels are shown in Table 1. Pembrolizumab will be administered on Day 1 approximately 60 to 90 minutes after infusion of LV is complete.

Only 1 dose escalation cohort will be open at a time. DLT evaluation will only include data from dose-escalation cohorts and will be assessed according to the DLT criteria in Section 3.1.5. Other dose levels may be evaluated based on the totality of the safety data and/or recommendations from the SMC.

The SMC will monitor safety during dose escalation in Part C and may recommend expansion of any cohort to further evaluate the safety at a given dose or enrollment of additional cohorts to investigate intermediate or additional dose levels of LV. The SMC will continue to review cumulative safety data in order to identify safety concerns that may emerge due to cumulative exposure, after the DLT window, or at a low frequency. In addition, the SMC will assess AE data from patients in dose-expansion cohorts to identify safety signals. For more details, see Section 7.5.1.

Dose escalation will be guided by the modified toxicity probability interval (mTPI) method (Ji 2010). The mTPI method is a model-based dose-escalation design that uses a Bayesian statistical framework and a beta-binomial hierarchic model (see Appendix M for more details and scenarios). Using a target DLT rate of 25% with a 5% margin, the dosing-decision rules are:

1. Escalate if current DLT rate is most likely <20%
2. Continue if current DLT rate is most likely between 20% and 30%
3. De-escalate if current DLT rate is most likely >30%

Each dose cohort will start with 2 patients. The SMC will evaluate the safety of each dose-level cohort and make dose escalation/de-escalation recommendations using the decision matrix in Table 2. Escalation to the next dose level will occur if 0 of 2 evaluable patients encounter a DLT. If 1 of 2 evaluable patients encounter a DLT, an additional 4 patients will be accrued (total of 6 DLT-evaluable patients). If 2 of 2 evaluable patients at a dose level encounter a DLT, further evaluation of that dose level may be allowed if recommended by the SMC. Escalation to the next dose level will occur if ≤1 of 6 evaluable patients encounter a DLT (see Table 2, column 5). The

MTD will be estimated based on data from all patients across all evaluated dose levels (Appendix M). If no doses are safe, dose escalation will stop, and no MTD will be declared.

The sponsor (in consultation with the SMC) may, for safety reasons, override the model's allocation of a patient to a particular dose level.

Table 1: Planned dose levels for Part C (q1wk LV dosing)

Dose Level	Weekly LV Dose (mg/kg/wk)	Maximum LV dose in a 3-week cycle (mg/kg/cycle)
0	1.00	3.00
1	1.25	3.75

The maximum dose will be 200 mg per infusion at all dose levels.

Table 2: mTPI decision matrix

	Number of DLT-Evaluable Patients Treated at Current Dose								
Number of Patients with DLTs		2	3	4	5	6	7	8	9
	0	E	E	E	E	E	E	E	E
	1	S	S	S	S	E	E	E	E
	2	D[a]	D	D	S	S	S	S	S
	3		DU	DU	DU	D	S	S	S
	4			DU	DU	DU	DU	DU	D
	5				DU	DU	DU	DU	DU
	6					DU	DU	DU	DU
	7						DU	DU	DU
	8							DU	DU
	9								DU

E=Escalate to the next higher dose, S=Stay at the current dose, D=De-escalate to the next lower dose, DU=Current dose is unacceptably toxic.

a Dose will be de-escalated if the first 2 DLT-evaluable patients in a dose level experience a DLT. Further evaluation of that dose level may be allowed if recommended by the SMC.

3.1.3.2. Part C: Expansion Cohort

Expansion cohorts may be opened at any dose level that has cleared DLT evaluation. Up to approximately 60 patients will be enrolled in expansion cohorts.

The totality of data from all patients in dose escalation and expansion will be used to determine the recommended q1wk LV dose. After the q1wk dose has been determined, additional patients may be enrolled at the recommended dose.

3.1.4. Part D: Day 1 and Day 8 every 21-days LV dosing

Part D will assess LV 1.5 mg/kg administered on Day 1 and Day 8 (**off** Day 15) of every 21-day cycle, not to exceed 200 mg per infusion, in combination with pembrolizumab administered on Day 1 of every cycle. Approximately 40 patients with PD-L1 CPS<10 will be enrolled in Part D. Ongoing, real-time, continuous review of patient safety and SAEs will be conducted by the sponsor's Drug Safety Department. Additionally, the ISMC will ensure periodic safety data review throughout the study.

3.1.5. Dose-Limiting Toxicity

DLTs are only assessed during Part A and dose escalation cohorts in Part C of the study.

The DLT-evaluation period is the first treatment cycle in Part A and Part C dose escalation. Patients who experience a DLT in Cycle 1 should not receive further treatment with LV and pembrolizumab, unless clinical benefit is demonstrated with adequately managed toxicity. Subsequent doses will be defined by the medical monitor in discussion with the site investigator, in the context of the type of AE observed.

The IBs for LV and pembrolizumab individually describe AEs commonly observed relative to either agent, as well as less common serious findings. The respective IBs should be referenced when attributing causality; however, the final decision regarding causality is at the discretion of the investigator.

If any patient enrolled in Part A or Part C dose escalation discontinues the study without DLT during the DLT period, another patient may be enrolled at the same dose level for DLT evaluation. However, the original patient will be included in the safety analysis.

No DLT evaluation will be conducted in Part D, because no DLT was observed with LV 1.5 mg/kg weekly dosing in SGNLVA-001 (see Section 3.2.3.4). Furthermore, pharmacokinetic exposure of LV given 1.5 mg/kg on Days 1 and 8 every 3 weeks will not surpass LV given 1.5 mg/kg weekly.

3.1.5.1. Dose-Limiting Toxicity in Part A

A DLT in Part A is defined as 1 of the following that is considered related to LV or the combination, and cannot be attributed to pembrolizumab alone:

- Any clinically significant, non-hematologic AE ≥ Grade 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (exceptions noted in list below)
- ≥ Grade 3 febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with clinically significant bleeding that requires medical intervention
- Grade 4 anemia unrelated to underlying disease
- Discontinuation during Cycle 1 due to treatment-related toxicity
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Grade 5 event (death)

The following events will not be considered a DLT:

- Grade 3 fatigue that improves to ≤ Grade 1 within 3 days with or without medical assessment
- Grade 3 tumor pain that improves to ≤ Grade 1 within 3 days with or without medical assessment

- LV infusion: Grade 3 infusion-related reactions (IRRs) that resolve within 1 day with or without medical assessment
- ≥ Grade 3 non-hematological laboratory abnormalities that resolve to ≤ Grade 1 within 7 days with or without optimal medical management
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities and Grade 3 elevations in blood glucose not associated with clinical sequelae that are corrected with supplementation/appropriate management within 3 days
- Grade 3 rash that improves to ≤ Grade 2 within 3 days with or without medical assessment
- Grade 3 nausea that improves to ≤ Grade 1 within 3 days with or without medical assessment
- Grade 3 diarrhea that improves to ≤ Grade 1 within 3 days with or without medical assessment
- Grade 3 vomiting that improves to ≤ Grade 1 within 3 days with or without medical assessment

The following event will not be considered DLT evaluable:

- Pembrolizumab infusion: ≥ Grade 3 IRRs – these patients must be discontinued from pembrolizumab (see Sections 5.3.5, 9.3.1.7), and are not evaluable for DLTs.

3.1.5.2. Dose-Limiting Toxicity in Part C

A DLT in Part C is defined as 1 of the following that is considered related to LV or the combination, and cannot be attributed to pembrolizumab alone:

- Any clinically significant, non-hematologic AE ≥ Grade 3 according to the NCI CTCAE, Version 4.03 (exceptions noted in list below)
- ≥ Grade 3 febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with clinically significant bleeding that requires medical intervention
- Grade 4 anemia unrelated to underlying disease
- Discontinuation during Cycle 1 due to treatment-related toxicity
- Inability to receive all 3 doses of LV (Days 1, 8, and 15) due to patient not meeting dosing criteria (see Section 5.2.3.5)
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Grade 5 event (death)

The following events will not be considered a DLT:

- Grade 3 fatigue that improves to ≤ Grade 1 within 3 days with or without medical assessment
- Grade 3 tumor pain that improves to ≤ Grade 1 within 3 days with or without medical assessment

- LV infusion: Grade 3 IRRs that resolve within 1 day with or without medical assessment
- ≥ Grade 3 non-hematological laboratory abnormalities that resolve to ≤ Grade 1 within 7 days with or without optimal medical management
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities and Grade 3 elevations in blood glucose not associated with clinical sequelae that are corrected with supplementation/appropriate management within 3 days
- Grade 3 rash that improves to ≤ Grade 2 within 3 days with or without medical treatment
- Grade 3 nausea, diarrhea or vomiting that improves to ≤ Grade 1 within 3 days with or without medical treatment

The following event will not be considered DLT evaluable:

- Pembrolizumab infusion: ≥ Grade 3 IRRs – these patients must be discontinued from pembrolizumab (see Sections 5.6.1.2, 5.6.1.3) and are not evaluable for DLTs.

Patients who do not complete the 21-day DLT evaluation period for reasons other than DLT will not be considered for dose-escalation decisions and/or determination of the MTD. Patients who are considered non-evaluable for dose-escalation decisions and/or MTD and will be replaced at the same dose level.

3.2. Discussion and Rationale for Study Design

The FDA's "Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (May 2007) was considered prior to the selection of primary and secondary endpoints for this study. The endpoints of this study are appropriate for evaluating the safety of LV treatment in combination with pembrolizumab for patients with LA/M TNBC. Standardized RECIST v1.1 criteria (Eisenhauer 2009) (Appendix J), and iRECIST guidelines (Seymour 2017) (Appendix K) when applicable, will be employed by investigators to evaluate responses and determine subsequent treatment. In this patient population, where the majority of the patients who respond to the antitumor therapy achieve PR, ORR, as a direct measure of antitumor activity, is the most appropriate endpoint to assess treatment benefit. The primary endpoint of ORR as assessed by RECIST v1.1 allows a direct comparison of this study with reported immunotherapy trials that have also used RECIST v1.1, as well as with chemotherapy trials.

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may therefore not provide an accurate response assessment of immunotherapeutic agents. Therefore, in addition to RECIST, this study will employ immune-modified RECIST (iRECIST) for tumor assessments to account for the appearance of possible new lesions and allow radiographic progression to be confirmed at a subsequent assessment.

To further assess the significance of ORR in this study, the durability of response will be evaluated as a secondary endpoint.

The DLT evaluation in Part A of the study will provide an opportunity to assess safety and tolerability of the combination treatment, the components of which have previously been assessed for safety in other settings and will also provide an opportunity to determine the MAD for Part B of the study. The starting dose for LV in Part A is 2.5 mg/kg q3wk (capped at 80 kg prior to Amendment 2 or 100 kg under Amendment 2 and later). If this dose level is not tolerated, a step-down dose level at 2.0 mg/kg q3wk is included in the study design and may be tested. The dose expansion part (Part B) will provide additional safety data for combining q3wk LV with pembrolizumab. Pembrolizumab will be administered at the standard dose. An SMC and ISMC will monitor safety, and the safety endpoints are appropriate for evaluating the safety of the combination regimens.

Part C will evaluate the safety and efficacy of LV when administered in more frequent, lower doses than those tested in Parts A and B. Dose finding in Part C will use the mTPI method (see Sections 3.1.3.1 and 3.2.3.3).

Part D will evaluate the safety and efficacy of LV 1.5 mg/kg when administered on Days 1 and 8 (**off Day 15**) of every 21-day cycle in combination with pembrolizumab administered on Day 1 of every cycle.

To better understand relationships between pre-treatment BC's biological characteristics and patient outcome, a freshly obtained pretreatment tumor biopsy (or archival tissue collected after the most recent cytotoxic therapy) will be used for biomarker assessments. Biomarker assessments will not be used for patient selection (with the exception of PD-L1 for Part D patients) because it is currently unknown if biomarker expression will impact outcome.

3.2.1. Method of Assigning Patients to Treatment Groups

Following informed consent and screening assessments, patients will be enrolled into Part A, Part B, and Part C sequentially. Patients will enroll in Part B Cohort 1 and Part B Cohort 2 sequentially. In this open-label, single-arm study, enrollment and treatment in Part A will be completed before enrollment begins in Part B. The safety and tolerability of the combination treatment will be evaluated, and a MAD will be determined by an SMC prior to expansion of enrollment to evaluate treatment effect in Part B. Opening of and enrollment in Part B will be determined by the sponsor.

In Part C, if a dose-escalation cohort and an expanded lower-dose cohort are concurrently open for enrollment, patients will be preferentially enrolled to the dose-escalation cohort. Multiple expansion cohorts may be opened concurrently; cohort assignment will be determined by the sponsor. The cohort assignments and decisions will be documented in the clinical trial master file.

In Part D, enrollment will be continuous without pause. No DLT evaluation will be conducted in Part D, because no DLT was observed with LV 1.5 mg/kg weekly dosing in SGNLVA-001 (see Section 3.2.3.4). Furthermore, pharmacokinetic exposure of LV given 1.5 mg/kg on Days 1

and 8 every 3 weeks will not surpass LV given 1.5 mg/kg weekly. Ongoing, real-time, continuous review of patient safety and SAEs will be conducted by the sponsor's Drug Safety Department. Additionally, the ISMC will ensure periodic safety data review throughout the study.

3.2.2. Rationale for Selection of q3wk Doses

Although pembrolizumab and LV had not been combined prior to this study, the MMAE payload (as part of the drug brentuximab vedotin) had been tested with the PD-1 inhibitor nivolumab in patients with HL in a Phase 1/2 trial (Herrera 2016). Of 42 patients enrolled, fatigue was the most common AE occurring in 40% of patients, followed by nausea, IRR, pruritus, and rash. Potential immune-related adverse events (irAEs) included IRR (36%), rash (29%), diarrhea (26%), transaminase elevation (10%), and hypothyroidism (5%). All of these were Grade 1 and 2 except for 1 transaminase elevation event of Grade 3/4. There were no dose reductions or discontinuations due to AEs.

As the combination of brentuximab vedotin and nivolumab has demonstrated a manageable safety profile, the starting doses of pembrolizumab and LV will be at the full recommended dose of each molecule. Both LV and pembrolizumab are well tolerated with few overlapping Grade 3–5 toxicities. However, because of the potential for overlapping hepatic and gastrointestinal toxicities for pembrolizumab and LV, special caution will be taken by performing a planned safety evaluation after the first 6 patients have been followed through the end of the DLT period in Part A, or at the point that 2 or more patients experience a DLT, whichever comes first. The SMC will review all available data and make recommendations including dose de-escalation if indicated.

3.2.3. LV

Prior to Amendment 2, LV will be administered at 2.5 mg/kg on Day 1 of each 21-day cycle in this proposed phase 1b/2 study. Dosing is based on patient actual body weight, except for patients weighing >80 kg, where dosing will be based on an 80 kg maximum weight. For patients in Parts A and B treated under Amendment 2 and later, the maximum weight cap per infusion will be increased from 80 kg to 100 kg. Patients who receive >200 mg LV per infusion in Parts A and B are also required to be administered prophylactic G-CSF. This dose and regimen has demonstrated an acceptable safety profile and encouraging clinical activity in the phase 1 study (SGNLVA-001).

In SGNLVA-001, LV monotherapy was administered on Day 1 of each 21-day cycle. The study evaluated escalating dose levels of 0.5, 1.0, 1.5, 2.0, 2.5, and 2.8 mg/kg. An MTD was not reached in the dose-escalation part of study, and no DLTs were observed at any of the dose escalation levels. Treatment-emergent AEs reported in ≥30% of patients were fatigue, nausea, alopecia, decreased appetite, constipation, and peripheral neuropathy.

Incidence of neutropenia (Grade ≥3), including febrile neutropenia, increased with increasing dose levels.

An evaluation of safety events at 2.0 mg/kg (N=19) and 2.5 mg/kg with doses ≤200 mg (N=18) revealed no febrile neutropenic events or neutropenia-associated (SAEs), no Grade 5 events, and a similar rate of dose discontinuations/reductions in each cohort. Neutropenia was more common at LV 2.5 mg/kg; among the 11 patients who experienced SAEs, 5 patients had neutropenia. Febrile neutropenia occurred at 2.5 mg/kg with doses >200 mg in 2 of 11 patients. No other treatment-related deaths occurred on study. Dose modifications due to AEs were more common at 2.5 mg/kg with doses >200 mg.

Objective responses with monotherapy were only seen in mTNBC patients. Improved antitumor activity was observed with increasing dose levels of LV in heavily pretreated mTNBC patients. PRs have been observed in 14 of 42 evaluable patients treated at dose levels of 1.5 to 2.8 mg/kg. Confirmed PR, DCR, and median DOR were higher in the 2.5 mg/kg (≤200 mg) dose level compared to the 2.0 mg/kg dose level.

In summary, the proposed dose regimen of 2.5 mg/kg, on Day 1 of each 21-day cycle, is anticipated to provide a favorable balance of activity and safety observed in the phase 1 trial SGNLVA-001. To date, objective responses with monotherapy were seen in mTNBC patients. Improved antitumor activity was observed with increasing dose levels of LV in heavily pretreated mTNBC patients. PRs have been observed in 14 of 42 evaluable patients treated at dose levels of 1.5 mg/kg to 2.8 mg/kg. Confirmed PR, DCR, and median DOR were higher in the 2.5 mg/kg dose level compared to the 2.0 mg/kg dose level. Updated data suggested that the ORR might be higher for patients receiving >200 mg per cycle than those receiving ≤200 mg per cycle (Modi 2017) (Data on File). Thus, increasing the maximum weight cap per infusion to 100 kg, but requiring growth factor support for patients who will receive 200 to 250 mg per infusion, should provide a favorable balance of safety and activity for patients receiving LV.

3.2.3.1. Rationale for Part B Cohort 2 LV 2.0 mg/kg in Combination with Pembrolizumab

LV 2.5 mg/kg and 2.0 mg/kg in combination with pembrolizumab have both been tested in Part A, dose-finding phase. Preliminary data showed that the regimen at both LV dose levels was tolerable with manageable AEs. LV 2.5 mg/kg, the MAD, was further evaluated in Part B Cohort 1 expansion. Preliminary efficacy analysis of LV in combination with pembrolizumab demonstrate that the combination has comparable promising activity at the two investigated LV doses. Continuous monitoring by the ISMC suggested that LV 2.0 mg/kg may have better tolerability, albeit in a small sample size. While both LV doses are tolerable and have shown a manageable toxicity profile, opportunities remain to ensure the benefits of therapy are maximized. Amendment 4 aims to better assess tolerability and improve the risk-benefit profile of LV in combination with pembrolizumab through the addition of an expansion cohort at the lower LV 2.0 mg/kg dose.

3.2.3.2. Rationale for Selection of q1wk LV Doses in Combination with Pembrolizumab

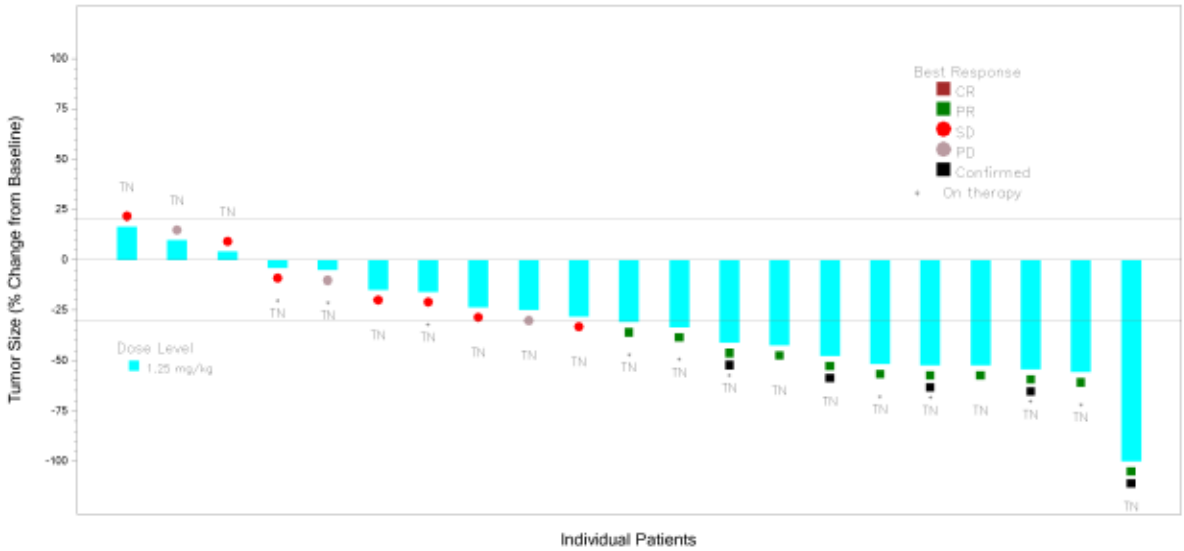
Multiple lines of evidence support that q1wk dosing may result in improved efficacy and safety of LV.

In Parts A and B of this study, as of 2 Dec 2019, a total of 88 patients had received LV at doses of 2.0 mg/kg or 2.5 mg/kg administered q3wk in combination with pembrolizumab. The combination has been shown to be active with a tolerable safety profile. The confirmed overall response rate was 40% amongst the efficacy evaluable patients (Data on File). No new safety signal was observed with the combination. Gastrointestinal AEs were predominant compared to other AEs. Most AEs were low to moderate grade in severity with nausea, fatigue, and alopecia being the most common AEs. The most common severe AEs (Grade 3 or 4) was neutropenia occurring in 13% of patients.

The starting dose of LV in Part C is 1.0 mg/kg/wk in combination with pembrolizumab. This LV dose results in a PK area-under-the-curve (AUC) exposure similar to LV of 2.5 mg/kg q3wk. At these similar PK exposures, it is not anticipated that there will be a detriment in the clinical efficacy or safety profile.

This is further supported by observations in Study SGNLVA-001 in which LV monotherapy q1wk doses of 1.0 and 1.25 mg/kg/wk were safely delivered without DLTs. Tumor size reductions in breast cancer patients were observed at the lowest dose level evaluated (1.0 mg/kg/wk). The most recent preliminary analyses of dose expansion cohort in study SGNLVA-001 (6-Jan-2021 data snapshot, Seagen Inc., data on file) demonstrated that most efficacy-evaluable patients with second-line mTNBC receiving LV 1.25 mg/kg q1wk had reductions in tumor size (Figure 3), demonstrating that LV administered q1wk has clinical activity against mTNBC.

Figure 3: Percent change in sum of tumor diameters for efficacy-evaluable patients with second-line mTNBC treated with a starting dose of 1.25 mg/kg q1wk



Source: 6-Jan-2021 data snapshot, Seagen Inc., data on file

At the time of the data snapshot, safety data were available for 52 patients who had received LV at 1.25 mg/kg q1wk. AEs observed at a greater than 30% incidence (any grade) in patients receiving LV 1.25 mg/kg q1wk included fatigue (56%), nausea (54%), peripheral sensory

neuropathy (44%), decreased appetite (42%), and constipation (33%). Most events were low grade. Common Grade 3 or higher AEs were neutropenia (17%), fatigue (14%), hyperglycaemia (11.5%), and hypophosphataemia (11.5%). This AE profile suggests that LV 1.25 mg/kg q1wk is tolerable and manageable.

In the initial 17 subjects treated with LV q1w + pembrolizumab in study SGNLVA-002 (data snapshot 7-Dec-2020), there was no emergence of new safety signals compared to LV q3w + pembrolizumab.

PK modeling data derived from over 200 patients previously treated with LV suggest improvements in the safety profile of LV q1wk dosing may be due in part to the reduced C_{max} compared to q3wk dosing (Data on File). In addition, LV q1wk dosing is anticipated to result in higher C_{trough} concentration levels (the lowest concentration reached by a drug before the next dose is administered), which are correlated with improved efficacy.

Other ADCs have been shown to have improved safety, activity, or both when administered at different doses and more frequent regimens than those originally tested. For example, trastuzumab emtansine (T-DM1), has improved efficacy with similar safety profiles when dosed q1wk compared to q3wk (Beeram 2012; Thuss-Patience 2017).

3.2.3.3. Rationale for mTPI Methodology in Part C

The mTPI dose escalation method, which has been used for dose finding in other oncology trials (Yap 2011; Ji 2013; Garrido-Laguna 2019), was chosen for this study because of the potential advantages it has over the traditional "3+3" approach for dose finding. In addition to providing the ability to estimate the MTD more accurately (Ji 2013; Ananthakrishnan 2017) (Appendix M), the mTPI approach enhances patient safety in several ways. First, the mTPI method uses information from all treated patients rather than only using data from the dose level under investigation. Second, fewer patients are treated above the MTD when compared to the traditional "3+3" approach (Ji 2013; Ananthakrishnan 2017). Third, by allowing flexible cohort sizes, the most appropriate patients can be exposed to study drug during dose escalation, providing higher power to identify safe and effective doses (Ji 2013).

3.2.3.4. Rationale for Selection of LV Dosing on Days 1 and 8 (off Day 15) in Every 21-day Cycle in Combination with Pembrolizumab in First-Line mTNBC With PD-L1 CPS<10 Patients in Part D

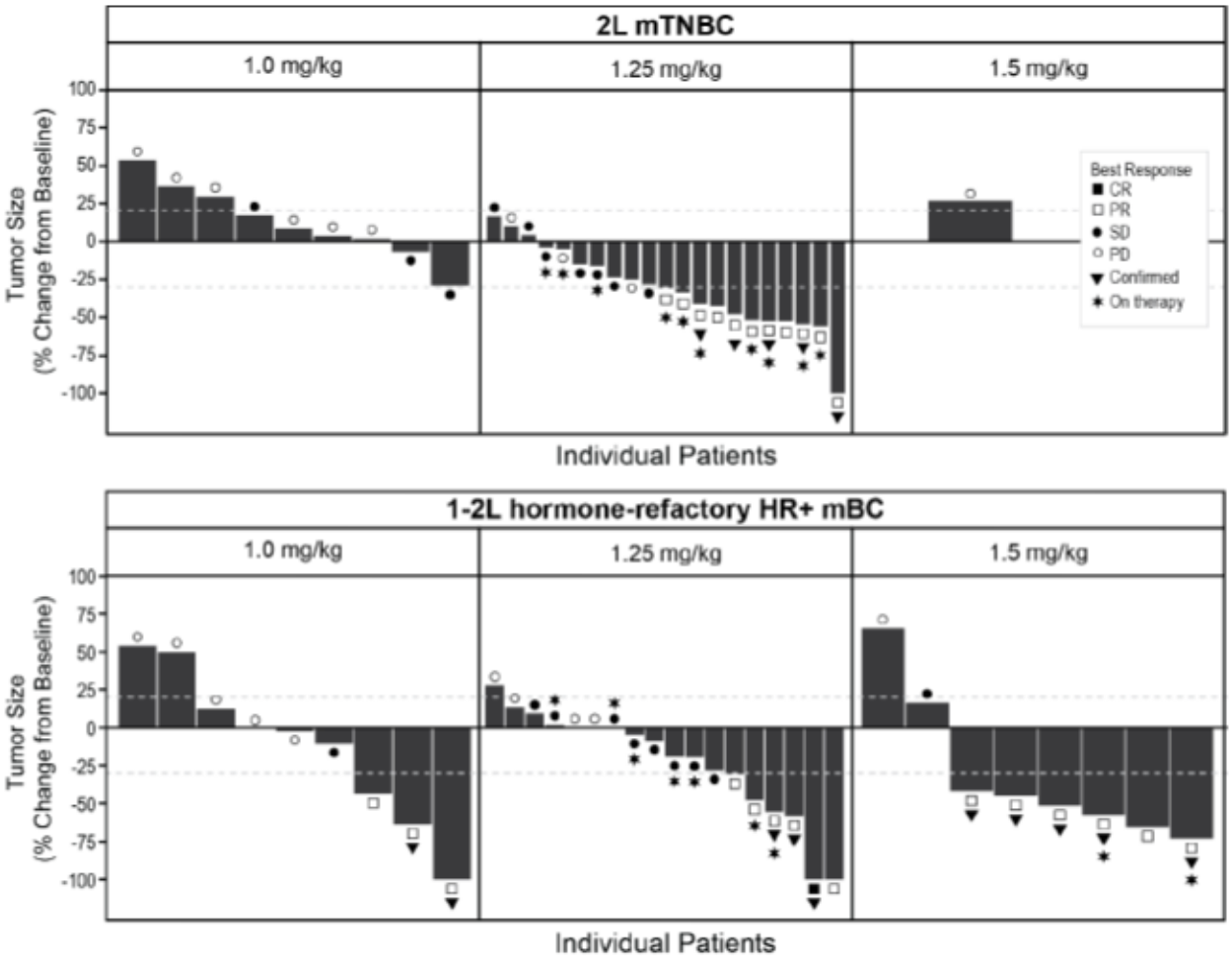
Study SGNLVA-001 Part E evaluates weekly LV monotherapy in patients with mTNBC or HR+/HER2- disease. Weekly LV monotherapy of 1.0 mg/kg. 1.25 mg/kg and 1.5 mg/kg were given on Day 1, Day 8, and Day 15 in every 21-day cycle. Up to approximately 82 patients (42 HR+/HER2- and 40 mTNBC) were planned for enrollment. During dose escalation, doses of LV ranging from 1.0 mg/kg up to 1.5 mg/kg were safely delivered without DLTs.

Preliminary efficacy data from Study SGNLVA-001 is shown in

Figure 4 below which demonstrates the best percentage change in the sum of tumor diameters from baseline (data cut 06-Jan-2021). While only one TNBC patient was dosed with LV

1.5 mg/kg q1wk, preliminary data in patients with HER2-/HR+ mBC showed dose-response correlation with increasing dose of LV q1wk.

Figure 4: Percent change in sum of tumor diameters by breast cancer subtype and dose



Source: Seagen, data on file (data cut 06-Jan-2021)

Even though better efficacy had been observed with 1.5 mg/kg, preliminary results led to 1.25 mg/kg being chosen for further expansion in Study SGNLVA-001 because of the higher frequency of neutropenia experienced at 1.5 mg/kg. Most of the clinically significant neutropenia occurred after 3 weekly doses at the 1.5 mg/kg dose level. These observations suggested that an LV dosing holiday may be needed to mitigate neutropenia.

Pharmacokinetic analysis of relative dosing intensity (RDI) with LV 1.25 mg/kg q1wk in monotherapy also showed that dose intensity started to decrease at Cycle 2, with dosing reduced to 2 doses in every 21-day cycle over time (Seagen data on file). This supports that a drug holiday could be beneficial for long-term treatment. Implementing a drug holiday may mitigate toxicities, reduce the need for dose modification, and therefore improve efficacy. This is further supported by PK simulation which demonstrated that giving LV 1.5 mg/kg on Days 1 and 8 every 21 days resulted in similar drug exposures as that of 1.25 mg/kg q1wk dosing

(Days 1, 8, and 15). Hence, administration of LV 1.5 mg/kg on Days 1 and 8 every 21 days may result in improved efficacy and safety of LV.

Part D will only enroll patients with PD-L1 CPS<10. Pembrolizumab + chemotherapy has received regulatory approval in the 1L advanced TNBC PD-L1 high (CPS≥10) subpopulation based on an overall survival benefit (Schmid 2018; Cortes 2020). Similar benefit was not observed in patients with PD-L1 CPS<10, where the standard of care remains chemotherapy and the outcomes are poor (response rates ~40% and median PFS about 5.5 months). Thus, these patients represent a population that continues to have high unmet medical need. This ongoing SGNLVA-002 study has demonstrated that LV + pembrolizumab not only is active against mTNBC but also can have a manageable safety profile suggesting that LV + pembrolizumab may provide an option for these patients.

3.2.4. Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg q3wk. Based on the totality of data generated in the Keytruda development program, 200 mg q3wk is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg q3wk to 10 mg/kg every 2 weeks (q2wk),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg q3wk across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg q3wk.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg q3wk versus 10 mg/kg q2wk (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg q3wk versus 10 mg/kg q2wk (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) q3wk provided similar responses to the highest doses studied. Subsequently, flat dose- and exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical HL, confirming 200 mg q3wk as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg q3wk. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of

PD-1 in systemic circulation at doses much lower than 200 mg q3wk. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg q3wk achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg q3wk fixed dose and 2 mg/kg q3wk dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg q3wk fixed-dose was selected for evaluation across all pembrolizumab protocols.

3.2.5. Blinding

This is an open-label study.

4. STUDY POPULATION

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1. Inclusion Criteria

1. Metastatic or locally-advanced, histologically documented TNBC (absence of HER2, estrogen receptor [ER], and progesterone receptor [PR] expression).
    a. HER2 negativity is defined as either of the following by local laboratory assessment (Wolff 2014):
        i. In situ hybridization non-amplified (ratio of HER2 to CEP17 <2.0 or single probe average HER2 gene copy number <4 signals/cell), or
        ii. IHC 0 or IHC 1+. If more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the medical monitor to establish eligibility of the patient.
    b. ER and PR negativity are defined as per current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines via IHC analysis.
    c. Part D only: Tumor tissue PD-L1 CPS <10 as determined by a PD-L1 IHC assay using the 22C3 clone.
2. Have not previously received cytotoxic therapy for the treatment of unresectable LA/M BC. Treatment with agents other than hormonally-directed/endocrine therapies will be counted as regimens.
3. For patients previously treated with curative intent, at least 6 months must have elapsed between the completion of such treatment (e.g., date of primary breast tumor surgery or date of last adjuvant cytotoxic therapy administration, whichever occurred last) and first documented local or distant disease recurrence.
4. Measurable disease as defined in RECIST v1.1: at least 1 tumor lesion ≥10 mm in the longest diameter, or a lymph node ≥15 mm in short axis measurement. Target lesions situated in a previously irradiated area are considered measurable only if they have shown unequivocal progression based on RECIST v1.1 after radiation therapy. Patients with bone-only metastatic lesions will be excluded.
5. Patients ≥18 years of age.
6. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
7. Able to provide adequate tissue obtained recently from a tumor lesion for biomarker analysis. Core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate.
    a. Note: Patients for whom recent/fresh samples cannot be obtained (e.g., inaccessible tumor or patient safety concerns) may submit an archived specimen in place of the

recent/fresh tissue if it was collected after completion of the patient's most recent cytotoxic therapy. If neither is available, please discuss with medical monitor.

8. The following baseline laboratory data:
   - absolute neutrophil count ≥1,500/μL
   - platelet count ≥100,000/μL
   - hemoglobin ≥8.0 g/dL
   - serum bilirubin ≤1.5x upper limit of normal (ULN) or ≤3x ULN for patients with Gilbert's disease
   - serum creatinine ≤1.5x ULN OR glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2 for patient with creatinine levels >1.5x institutional ULN. GFR calculation is found in Appendix N.
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5x ULN or ≤3x ULN if liver metastases are present
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5x ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
   - Activated partial thromboplastin time (aPTT) ≤1.5x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
9. For patients of childbearing potential as defined in Section 4.3, the following stipulations apply:
   a. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 3 days prior to the first dose of LV/pembrolizumab. Patients with false positive results and documented verification that the patient is not pregnant are eligible for participation.
   b. Must agree not to try to become pregnant from the time of enrollment until at least 6 months after the final dose of study drug. If heterosexually active, must consistently use 2 highly effective methods of birth control (as defined in Appendix G) during this time period.
   c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
10. Male patients under the following conditions:
   a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final study drug administration.
   b. If heterosexually active with non-pregnant, pregnant, or breastfeeding partner, must consistently use 2 highly effective methods of birth control (as defined in Appendix G) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.

11. Patient must provide written informed consent if they are able to. If a patient is unable to provide written informed consent, then written informed consent can be provided by a legally authorized representative (LAR) in accordance with local legal requirements.

4.2. Exclusion Criteria

12. Prior treatment with LV.

13. Prior immuno-oncology therapy (e.g., therapies affecting the PD-L1, PD-L2, CTLA-4, or CD137 pathways, or any other antibody or drug specifically targeting T cell costimulation or checkpoint pathways).

14. Pre-existing neuropathy of Grade ≥2.

15. History of another malignancy within 3 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., approximate 5-year OS of ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

16. History of carcinomatous meningitis or active central nervous system (CNS) metastases. Patients are eligible if CNS metastases are adequately treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to enrollment. In addition, patients must be completely off corticosteroids.

17. History of leptomeningeal carcinomatosis.

18. Active infection requiring systemic treatment ≤7 days before dose of study drug. Routine antimicrobial prophylaxis is permitted.

19. Known to be positive for hepatitis B by surface antigen expression, active hepatitis C infection (positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months), or a known history of being seropositive for HIV. Patients who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.

20. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with congestive heart failure, Class III-IV, by New York Heart Association criteria within 6 months prior to study enrollment (See Appendix I).

21. Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior treatment including systemic therapy, radiotherapy, or surgery.

22. Has received prior radiotherapy within 2 weeks of start of study treatment. A patient is also excluded if radiotherapy occurred more than 2 weeks prior to start of study treatment but the patient has not recovered from radiation-related toxicities, requires corticosteroids, or has had radiation pneumonitis.

23. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
24. History of interstitial lung disease.
25. Current pneumonitis, or history of (non-infectious, including radiation induced) pneumonitis that required steroids.
26. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of corticosteroids for physiological replacement may be approved after consultation with the sponsor.
27. Patients who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 6 months after final dose of study drug administration.
28. Known hypersensitivity to any excipient contained in the drug formulation of LV or pembrolizumab.
29. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to study Day 1.
30. Other serious underlying medical condition that, in the opinion of the investigator, would impair the ability to receive or tolerate the planned treatment and follow-up; any psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the trial.
31. Has received a live vaccine within 30 days of planned start of study therapy.
    a. Note: seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines and are not allowed.
32. Has not recovered (e.g., to ≤ Grade 1 or to baseline) from AEs due to a previously administered therapy.
33. Has had an allogenic tissue/solid organ transplant.

4.3. Childbearing Potential

A patient of childbearing potential is defined as anyone born female who has experienced menarche and has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or completed menopause. Menopause is defined

clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological, physiological, or pharmacological causes.

4.4. Removal of Patients from Therapy or Assessment

Seagen or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and/or case report form (CRF).

4.4.1. Discontinuation of Study Treatment

A patient's study treatment may be discontinued for any of the following reasons:

- Progressive disease (PD)
- AE
- Pregnancy
- Investigator decision
- Patient decision, non-AE
- Study termination by sponsor
- Other, non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

Discontinuation of pembrolizumab may be considered for patients who have attained a confirmed CR that has been treated for at least 8 cycles (24 weeks) and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

Patients who discontinue pembrolizumab may continue to receive LV with medical monitor approval (see Section 5.2.5). Similarly, patients that discontinue LV may continue to receive pembrolizumab with medical monitor approval (see Section 5.3.5).

4.4.2. Patient Withdrawal from Study

Any patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by sponsor
- Completion of protocol specified safety follow-up (see Section ●)
- Lost to follow-up
- Death
- Other

5. TREATMENTS

5.1. Treatments Administered

All patients will receive LV, the investigational agent under study in this protocol, in combination with pembrolizumab. LV will be administered first, followed by pembrolizumab approximately 60–90 minutes after infusion of LV is complete.

5.2. Investigational Study Drug: LV

LV is an ADC consisting of the anti-LIV1A mAb hLIV22 conjugated to MMAE, a synthetic analog of the naturally occurring tubulin-binding agent, dolastatin 10.

Detailed information describing the preparation, administration, and storage of LV is located in the LV Pharmacy Instructions.

5.2.1. Description

LV is a sterile, preservative-free, white to off-white lyophilized cake or powder for reconstitution for IV administration. LV is supplied by Seagen in single-use glass vials. Each drug product vial contains LV for Injection, trehalose, histidine, and polysorbate 80. Drug product vials are labeled with a nominal content of 40 mg/vial. Each vial contains 45 mg of LV. Enough overfill is included to allow for 40 mg of LV to be withdrawn for use.

When reconstituted with 8.8 mL Water for Injection (WFI), United States Pharmacopeia (USP), the concentration of reconstituted LV product is 5 mg/mL. The reconstituted drug product is a clear to slightly opalescent, colorless to light yellow solution with no visible particulate matter. The pH is approximately 6.0. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, USP, for IV administration.

5.2.2. Method of Procurement

LV will be provided by the sponsor.

5.2.3. Dose and Administration

5.2.3.1. All Parts

In the absence of IRRs, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

LV must not be administered as an IV push or bolus. LV should not be mixed with other medications.

Weight-based dosing of LV is based on the patient's actual body weight. Doses must be adjusted for patients who experience a ≥10% change in weight from baseline. Patient weight must be measured during all relevant assessment windows as described in the schedule of events (Appendix A). If weight is assessed per institutional standard of care at a timepoint not required per protocol (e.g., Day 8 or Day 15) and there is a ≥10% change in weight from baseline, LV

dose must be adjusted accordingly. Other dose adjustments for changes in body weight are permitted per institutional standard.

5.2.3.2. Parts A and B

Prior to Amendment 2, LV at a dose of 2.5 mg/kg (capped at 80 kg per infusion) will be administered on Day 1 of every 21-day cycle by IV infusion given over approximately 30 minutes. For patients treated under Amendment 2 and later, the maximum weight cap per infusion will be increased from 80 kg to 100 kg. Any patient receiving >200 mg LV per infusion (weight >80 kg) is required to receive prophylactic G-CSF. For patients weighing ≥100 kg, dosing will be based on 100 kg. In consultation with the sponsor, eligible patients already on treatment prior to Amendment 2, may have their maximum weight cap per infusion increased to 100 kg or remain at 80 kg if they are receiving benefit (CR, PR, or SD).

Prior to Amendment 2, for patients weighing greater than 80 kg, dose calculations will be based on 80 kg (including dose reductions). **For patients treated under Amendment 2 and later, the maximum weight cap per infusion will be increased from 80 kg to 100 kg, therefore, the maximum dose will be 250 mg per infusion when dosing at 2.5 mg/kg and 200 mg per infusion when dosing at 2.0 mg/kg.** For patients who receive >200 mg LV per infusion, prophylactic G-CSF administration is required and will be given to patients on the day after study treatment is given, with a visit window of Day 2–4. Rounding is permissible within one milligram of nominal dose.

5.2.3.3. Part C

LV will be given on Day 1, Day 8, and Day 15 in every 3-week cycle.

At least 7 days must elapse between administrations of LV. There will be no weight cap per infusion. The maximum dose will be 200 mg per infusion.

5.2.3.4. Part D

LV will be given at a dose of 1.5 mg/kg by IV infusion over approximately 30 minutes on Day 1 and Day 8 in every 21-day cycle. LV will **NOT** be administered on Day 15 for patients enrolled in Part D.

At least 7 days must elapse between administrations of LV. The maximum dose will be **200 mg** per infusion.

5.2.3.5. LV Dosing Criteria

Dose modification guidelines for LV are detailed in Table 3 and Table 6. The following laboratory criteria must be met on Day 1 of each cycle prior to LV administration:

- Neutrophil count ≥1000/μL (≤ Grade 2)
- AST ≤ Grade 2
- ALT ≤ Grade 2
- Total bilirubin ≤ Grade 2
- Blood glucose ≤250 mg/dL or ≤13.9 mmol/L

If these criteria are not met on the day of dosing, hold the LV dose until criteria are met. In addition, hold LV dosing for patients with ≥ Grade 2 peripheral neuropathy. Additional information on LV dose modifications can be found in Table 3 and Table 6. Please see Table 7 for information on pembrolizumab dosing.

In Part C, neutrophil count must also be ≥1000/μL (≤ Grade 2) prior to LV administration on Days 8 and 15 of each cycle.

In Part D, neutrophil count must also be ≥1000/μL (≤ Grade 2) prior to LV administration on Day 8 of each cycle.

5.2.4. Overdose

In the event of an overdose >10% of LV, the site should notify the sponsor as soon as they are aware of the overdose. The patient should be closely monitored for adverse reactions, particularly neutropenia. Supportive care per institutional standards should be administered. Adherence to current clinical practice guidelines for the use of white blood cell (WBC) growth factors (see Appendix L) is strongly recommended for the management of neutropenia and febrile neutropenia (Crawford 2010; Smith 2015).

5.2.5. Dose Modifications

Patients who experience DLT in Cycle 1 (the DLT evaluation period) should not receive further treatment with LV and pembrolizumab unless clinical benefit is observed, and the AE(s) is adequately managed with severity improving to Grade 1 or lower. Subsequent doses will be defined by the medical monitor in discussion with the site investigator in the context of the type of AE(s) observed.

In the event a patient is unable to tolerate their dose level, additional treatment cycles (Cycle 2 or later) may be administered at a lower dose level. Consultation with the medical monitor is strongly encouraged.

Patients who discontinue pembrolizumab due to a pembrolizumab-related AE may continue LV. Similarly, patients who discontinue LV for a LV-related AE may continue pembrolizumab.

5.2.5.1. Parts A and B

If a patient has a clinically significant, unresolved AE on Day 1 of any cycle, the start of the cycle may be delayed for up to 14 days. Delays of >14 days must be approved by the medical monitor.

Dose modifications for LV treatment associated toxicity are described in Table 3. Any deviations from these modifications should be discussed with the medical monitor.

Prior to Amendment 2, the maximum doses after modification are:

- 160 mg for patients reduced to 2.0 mg/kg
- 120 mg for patients reduced to 1.5 mg/kg

For patients treated under Amendment 2 and later, the maximum doses after modification are:

- 200 mg for patients reduced to 2.0 mg/kg
- 150 mg for patients reduced to 1.5 mg/kg
- 125 mg for patients reduced to 1.25 mg/kg

Table 3: Required dose modifications for LV-associated toxicities (Parts A and B)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy[a]	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 1; then resume treatment at the next lower dose level	Withhold until toxicity resolves to ≤ Grade 1, then resume treatment at the next lower dose level	Discontinue treatment
Hyperglycemia	Hold for glucose >250 mg/dL or >13.9 mmol/L. Testing may be repeated on the same day of dosing. Dose may be delivered on the same day once elevated blood glucose has improved to ≤250 mg/dL or ≤13.9 mmol/L and patient is clinically and metabolically stable.			
Non-hematologic[a] (except peripheral neuropathy and elevated blood glucose)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at same dose level[b]	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to the next lower dose level and resume treatment, or discontinue at the discretion of the investigator[b,c]
Hematologic[a]	Continue at same dose level	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 2 or baseline.[d,e] **For neutropenia, strongly consider WBC Growth Factor support,** then resume treatment at the same dose level. **Prophylactic WBC Growth Factor support should be strongly considered for subsequent cycles.** (See Appendix L)	Withhold until toxicity resolves to ≤ Grade 2 or baseline.[d,e] **For neutropenia, strongly consider WBC Growth Factor support,** then resume treatment at the same dose level. **Prophylactic WBC Growth Factor support is required for all subsequent cycles.** If Grade 4 neutropenia recurs despite WBC Growth Factor support, consider dose reduction to 2.0 mg/kg or discontinuation (See Appendix L)
Febrile neutropenia[a]			WBC Growth Factor support is required for treatment of febrile neutropenia. **Withhold until febrile neutropenia resolves and neutrophil count returns to ≤ Grade 2 or baseline then resume treatment at the same dose level.** Prophylactic WBC Growth Factor support is required for all subsequent cycles. **If febrile neutropenia recurs despite WBC Growth factor support, consider dose reduction to 2.0 mg/kg or discontinuation (See Appendix L)**	

Note: Prior to Amendment 2, for patients weighing >80 kg, dosing will be based on 80 kg. For patients treated under Amendment 2 and later, the maximum weight cap per infusion will be increased from 80 kg to 100 kg. Patients who receive >200 mg LV per infusion are also required to be administered prophylactic G-CSF.

a Only 2 dose reductions are allowed. Additional toxicities should be managed with dose delays.

b Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption if a management plan consistent with institutional practice and regular monitoring are put in place.

c Treatment should be discontinued for patients who experience Grade 4 IRRs.

d Support with blood product transfusions allowed per institutional standard of care.

e Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.5.2. Part C (q1wk LV dosing)

Dose modification guidelines for LV for selected AEs are detailed in Table 6.

If a patient has an AE or lab criterion that prevents dosing on Day 1 of any cycle, the start of the cycle may be delayed for up to 14 days. Delays of >14 days must be approved by the medical monitor.

In the event of an AE or lab criterion that prevents dosing of LV during the cycle (e.g., Day 8 or 15, Section 5.2.3.5), the LV dose for the week should be withheld up to 4 days. LV may be resumed when the dosing criteria are met.

If a dose(s) of LV is withheld, the corresponding visit may be skipped and resume at the following week (e.g., if the Day 8 dose is skipped, visits will resume on Day 15; if Day 15 dose is skipped, visits will resume on Day 1 of the following cycle).

Dose reduction of LV may be considered in the event of recurrent AE despite withheld doses. Dose re-escalation following dose reduction is not allowed. Dose levels for LV dose reductions in Part C are shown in Table 4.

Table 4: Q1wk LV dose reductions for Part C

Starting dose	First dose reduction (mg/kg/wk)	Second dose reduction (mg/kg/wk)
Dose level 0 (1.0 mg/kg/wk)	0.75	0.5
Dose level 1 (1.25 mg/kg/wk)	1.0	0.75

For nonclinical events requiring alteration in dosing schedule (e.g., holidays, scheduling conflicts), a +2-day dosing window is allowed. If more than a +2-day window is needed, the medical monitor must be consulted. The medical monitor must approve skipped dose(s) for nonclinical events. At least 7 days must elapse between administrations of LV.

5.2.5.3. Part D (Day 1 and Day 8 LV dosing)

Dose modification guidelines for LV for selected AEs are detailed in Table 6.

If a patient has an AE or lab criterion that prevents dosing on Day 1 of any cycle, the start of the cycle may be delayed for up to 21 days. Delays of >21 days must be approved by the medical monitor.

In the event of an AE or lab criterion that prevents dosing of LV on Day 8 during the cycle (e.g., Section 5.2.3.5), the LV dose for the week may be withheld up to 4 days. LV may be resumed when the dosing criteria are met. If a dose of LV is withheld for more than 4 days, the corresponding visit may be skipped and dosing resumed at the following visit (eg, if the Day 8 dose is skipped, visits will resume on Day 1 of the following cycle).

Dose reduction of LV may be considered in the event of recurrent AE despite withheld doses. Dose re-escalation following dose reduction is not allowed. Dose levels for LV dose reductions in Part D are shown in Table 5.

Table 5: LV dose reductions for Part D

Starting dose	First dose reduction	Second dose reduction[a]
1.5 mg/kg	1.25 mg/kg	1.00 mg/kg[b]

f If patients have more than 2 dose reductions (with medical monitor approval), dose will be the next appropriate reduced dose level determined by discussion between investigator and medical monitor.

g The dose may be reduced to 0.75 mg/kg/week following approval from the medical monitor.

For nonclinical events requiring alteration in dosing schedule (e.g., holidays, scheduling conflicts), a +4-day dosing window is allowed. If more than a +4-day window is needed, the medical monitor must be consulted. The medical monitor must approve skipped dose(s) for nonclinical events. At least 7 days must elapse between administrations of LV.

Table 6: Dose modifications for LV treatment-related adverse events (Parts C and D)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy[a]	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 1; treatment may resume at the next lower dose level (see Table 4 for Part C or Table 5 for Part D)	Withhold until toxicity resolves to ≤ Grade 1, then resume treatment at the next lower dose level (see Table 4 for Part C or Table 5 for Part D)	Discontinue treatment
Hyperglycemia	Hold for blood glucose >250 mg/dL or >13.9 mmol/L. Resume treatment once elevated blood glucose has improved to ≤250 mg/dL or ≤13.9 mmol/L and subject is clinically and metabolically stable (see Section 5.7 for details).			
Non-hematologic[a] (except peripheral neuropathy and elevated blood glucose)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at same dose level[b]	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to the next lower dose level (see Table 4 for Part C or Table 5 for Part D) and resume treatment, or discontinue at the discretion of the investigator[b,c]
Hematologic[a]	Continue at same dose level	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 2 or baseline[d,e], then resume treatment at the same dose level. If the dose is held >48 hours, the dose may be omitted and dosing may resume on the next scheduled dosing day. See Sections 5.5.2 and 5.5.2.1 on allowed concomitant therapy and myeloid growth factors.	Withhold until toxicity resolves to ≤ Grade 2 or baseline[d,e], then reduce dose to the next lower dose level (see Table 4 for Part C or Table 5 for Part D) if treatment is resumed[b,c]. If the dose is held >48 hours, the dose may be omitted and dosing may resume on the next scheduled dosing day. If Grade 4 neutropenia recurs, reduce dose to the next lower dose level (see Table 4 for Part C or Table 5 for Part D) if treatment is resumed, or discontinue at the discretion of the investigator. See Sections 5.5.2 and 5.5.2.1 on allowed concomitant therapy and myeloid growth factors.
Febrile neutropenia[a]	Not applicable	Not applicable	Withhold until febrile neutropenia resolves and neutrophil count returns to ≤ Grade 2 or baseline and then resume treatment at the next lower dose level (see Table 4 for Part C or Table 5 for Part D). If the dose is held >48 hours, the dose may be omitted and dosing may resume on the next scheduled dosing day. If febrile neutropenia recurs, reduce dose to the next lower dose level (see Table 4 for Part C or Table 5 for Part D) if treatment is resumed, or discontinue at the discretion of the investigator. See Sections 5.5.2 and 5.5.2.1 on allowed concomitant therapy and myeloid growth factors.	

The maximum dose will be 200 mg per infusion for patients enrolled in Parts C and D.

a Only 2 dose reductions are allowed without prior medical monitor approval. Additional toxicities should be managed with dose delays. Medical monitor approval is needed for further dose reduction.

b Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption if a management plan consistent with institutional practice and regular monitoring are put in place.

c Treatment should be discontinued for patients who experience Grade 4 infusion-related reactions.

d Support with blood product transfusions allowed per institutional standard of care.

e Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.6. Storage and Handling

Single-use vials containing LV must be stored under refrigeration at 2–8°C in an appropriate secured area accessible only to the pharmacist, investigator, or a duly designated person.

Chemical and physical stability of the reconstituted drug product has been demonstrated for 24 hours at 2–8°C and at room temperature. However, LV drug product does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours under refrigeration at 2–8°C. The prepared dosing solution (reconstituted drug product solution and saline dilution in an IV bag or polypropylene syringe) should be administered within 8 hours after exposing to ambient temperature and light condition.

It is recommended that the drug product vials and solutions be protected from direct sunlight until the time of use.

Do not shake reconstituted LV.

Any partially used vials or prepared dosing solutions should be discarded by the site according to institutional drug disposal procedures. Unused vials may only be discarded by the site after authorization by the sponsor.

5.2.7. Packaging and Labeling

LV is supplied in glass vials. The drug product vials are labeled as LV, the compound code. Refer to the Pharmacy Instructions for a sample label of LV.

5.2.8. Preparation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Before administration, LV must be reconstituted and diluted. Diluted solutions of LV are stable at a concentration range of 0.3 mg/mL to 2.5 mg/mL. The formulation contains no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Mixing of lot/batch numbers is not allowed for preparation of a single dose; however, use of a different lot/batch number is allowed for subsequent doses during treatment cycles.

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.3. Pembrolizumab

Patients will receive pembrolizumab 200 mg in combination with LV.

5.3.1. Description

Pembrolizumab will be supplied as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of

pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine, polysorbate, sucrose, and WFI USP.

5.3.2. Method of Procurement

Pembrolizumab will be provided to all study sites by the sponsor. In countries outside the US, pembrolizumab will also be relabeled by the sponsor, to meet country-specific regulatory requirements.

5.3.3. Dose and Administration

NOTE: Study treatment should begin as close as possible to the date on which the patient is enrolled.

Study treatment of pembrolizumab will be administered on Day 1 of each 21-day cycle, after all procedures and assessments have been completed as detailed in Section 6 and Appendix A, Appendix B, and Appendix C.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion given approximately 60–90 minutes after administration of LV. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes –5 min/+10 min).

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

5.3.4. Overdose

For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of an overdose, the site should notify the sponsor as soon as they are aware of the overdose. The patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

5.3.5. Dose Modifications

5.3.5.1. Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

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

discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7.

Table 7: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action with pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor patients for signs and symptoms of pneumonitis Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor patients for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Patients with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5–1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg	

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action with pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
			prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a]	Initiate insulin replacement therapy for patients with T1DM Administer anti-hyperglycemic in patients with hyperglycemia	Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2–4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3, or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action with pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
All other irAEs	Persistent Grade 2	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue[b]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

GI=gastrointestinal; T1DM=Type 1 diabetes mellitus.

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

a The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

b Events that require discontinuation include, but are not limited to Guillain-Barre Syndrome, encephalitis, myelitis, Drug Rash with Eosinophilia and Systemic Symptom (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and other clinically important irAEs (e.g., vasculitis and sclerosing cholangitis).

5.3.5.2. Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8: Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Patient may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500–1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4	**Stop Infusion.**	No subsequent dosing
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study drug treatment.	

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

5.3.5.3. Other Allowed Dose Interruption for Pembrolizumab

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

Patients who discontinue LV due to an LV-related AE may continue pembrolizumab with approval of the medical monitor if there is evidence of clinical benefit. The maximum allowed number of pembrolizumab cycles is 35 (approximately 2 years).

5.3.6. Storage and Handling

Pembrolizumab should be stored and handled per the pharmacy manual.

5.3.7. Packaging and Labeling

Pembrolizumab is commercially available in the US.

5.3.8. Preparation

Pembrolizumab should be prepared per the pharmacy manual.

5.4. Required Premedication and Postmedication

Patients who experience a Grade 1 or Grade 2 IRR may receive subsequent infusions with premedication as described in Section 5.6.1. Prior to the first dose of LV, routine premedication should not be administered for the prevention of IRRs.

5.5. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.5.1. Required Concomitant Therapy

Patients in Parts A and B: Starting with Amendment 2, it is mandatory that patients in Parts A and B who are administered >200 mg LV per infusion receive prophylactic G-CSF treatment starting with their first cycle of therapy at a >200 mg LV dose. It is also strongly recommended that these patients continue to receive prophylactic G-CSF at subsequent cycles regardless of the LV dose, if it is deemed to be needed per investigators' clinical judgement. Therefore, patients receiving >200 mg LV must not have contraindications to myeloid growth factors and must be willing to receive them. Additionally, patients in Parts A and B who experience Grade 4 neutropenia or febrile neutropenia of any grade in any cycle, must receive myeloid growth factors in all subsequent cycles. Myeloid growth factor support is also required for treatment of febrile neutropenia in Parts A and B. As per ASCO guidelines, prophylactic growth factors should start 1-3 days after LV administration. Myeloid growth factors (including pegfilgrastim) should not be given within 24 hours prior to the dose of LV. If pegfilgrastim is used, a one-time dose is recommended. If daily growth factor support is used, treat for at least 5-7 days or until the absolute neutrophil count is >1000/mm^3 ($\leq$ Grade 2).

5.5.2. Allowed Concomitant Therapy

Patients may receive all supportive treatments according to the institutional standard.

All concomitant medications and blood products administered will be collected from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 7.5.1.6.

The use of antibiotics, when applicable, is allowed.

WBC growth factor support, including primary or secondary prophylaxis and treatment, is strongly encouraged per the ASCO 2015 Update (Smith 2015) (see Appendix L), with the exception of primary prophylaxis (Cycle 1 use) in patients enrolled in the dose escalation parts (with the exception of patients who receive >200 mg LV per infusion). Transfusions of blood products may be administered according to the institutional standard.

Patients should be up-to-date on any recommended vaccinations prior to study entry. Seasonal inactivated (killed) influenza vaccine is allowed. Additional vaccination during the course of the study treatment must be discussed prior to administration with the medical monitor.

If the patient is taking chronic suppressive or prophylactic anti-infectives (antiviral, antifungal, or antibacterial), documentation of investigations to ensure the absence of active infection must be completed prior to enrollment. The patient should continue suppressive or prophylactic anti-infectives for the duration of study participation.

Patients who are receiving P-glycoprotein (P-gp) or strong cytochrome P450 3A (CYP3A) inhibitors concomitantly with LV should be closely monitored for adverse reactions. Based upon evaluation of the anti-CD30 MMAE ADC brentuximab vedotin (Adcetris) (ADCETRIS® Prescribing Information, Seagen, June 2023), concomitant use of P-gp inhibitors or strong cytochrome P450 3A4 (CYP3A4) inhibitors has the potential to increase the exposure to MMAE (the cytotoxic component of LV and brentuximab vedotin). Concomitant use of P-gp inducers or strong CYP3A4 inducers could decrease exposure to MMAE. See Appendix H for a list of P-gp and CYP3A inducers and inhibitors.

Palliative radiotherapy (e.g., treatment for stable symptomatic metastasis) is permitted while on study treatment upon approval by the medical monitor provided it does not interfere with assessment of tumor response per RECIST v1.1, put the patient at risk for increased or worsened AEs, and is not being used to treat PD. Palliative radiotherapy should be given no sooner than 2 weeks before or 2 weeks after treatment with LV and pembrolizumab.

5.5.2.1. Myeloid Growth Factors

Myeloid growth factors (including pegfilgrastim) should not be given within 24 hours prior to any dose of LV. In Parts C and D, myeloid growth factor use is allowed per ASCO guidelines. However, for patients enrolled in Part C and D, long-acting myeloid growth factors (such as pegfilgrastim) may not be appropriate because LV is given either weekly or on Days 1 and 8 every 21 days. Long-acting myeloid growth factors should only be given when there is sufficient time for the growth factors to have cleared and for growth stimulatory activity to have ceased.

5.5.3. Prohibited Concomitant Therapy

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and LV
- Radiation therapy with the following exceptions:

- Radiation therapy to a symptomatic, non-target solitary lesion may be considered on an exceptional case-by-case basis after consultation with sponsor. The patient must have clear measurable disease outside the radiated field.
- Palliative radiation therapy may be allowed under the criteria outlined in Section 5.5.2.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
  - Note: Inhaled steroids are allowed for management of asthma.

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

Patients in Part C dose escalation cohorts should not receive prophylactic G-CSF in Cycle 1.

The Exclusion Criteria describe other medications that are prohibited in this trial.

There are no prohibited therapies during the post-treatment follow-up phase.

5.6. Management of Adverse Reactions

5.6.1. Management of Infusion Reactions

5.6.1.1. LV

IRRs may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. Routine premedication should not be administered for the prevention of IRRs prior to the first dose of LV.

All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs.

Patients who have experienced a Grade 1 or Grade 2 IRR with LV should be premedicated for subsequent infusions.

Patients who experience a Grade 3 IRR may potentially receive additional treatment with LV at the discretion of the investigator after discussion with the sponsor's medical monitor.

Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards.

If anaphylaxis or a Grade 4 IRR occurs, LV administration should be immediately and permanently discontinued.

5.6.1.2. Pembrolizumab

Please refer to the recommendations in Table 8.

5.6.1.3. Infusion Related Reaction of Uncertain Cause

If a patient experiences an IRR after receiving both study treatments and a single cause of the IRR cannot be determined, both sets of guidelines for IRRs must be followed.

5.6.2. Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.3.5, Table 7. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 5.3.5 for guidelines regarding dose modification and supportive care.

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

5.7. Management of Hyperglycemia

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, patients should be treated according to local standard of care and referral to endocrinology may be considered.

Patients, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose levels become difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

Patients who enter the study with elevated hemoglobin A1c (HbA1c) (≥6.5%) or fasting glucose (≥126 mg/dL or ≥7.0 mmol/L) at screening should receive glucose management prior to or within 1 week of starting study treatment.

In Part A and B, blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 mg/dL or >13.9 mmol/L, testing may be repeated on the same day of dosing. LV dose may be delivered on the same day once the patient's blood glucose has improved to ≤250 mg/dL or ≤13.9 mmol/L and the patient is clinically and metabolically stable.

In Part C, blood glucose may be checked on Day 8 and Day 15 by fingerstick as indicated, particularly in patients at risk for hyperglycemia. Day 8 and 15 dosing with LV should be withheld for blood glucose >250 mg/dL or >13.9 mmol/L. Testing may be repeated on the day of dosing. LV dose may be delivered on the same day once the patient's blood glucose has improved to ≤250 mg/dL or ≤13.9 mmol/L and the patient is clinically and metabolically stable.

In Part D, blood glucose may be checked on Day 8 by fingerstick as indicated, particularly in patients at risk for hyperglycemia. Day 8 dosing with LV should be withheld for blood glucose >250 mg/dL or >13.9 mmol/L. Testing may be repeated on the day of dosing. LV dose may be delivered on the same day once the patient's blood glucose has improved to ≤250 mg/dL or ≤13.9 mmol/L and the patient is clinically and metabolically stable.

5.8. Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents.

6. STUDY ACTIVITIES

6.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.5.1.3). Any study protocol-related AE (defined in Section 7.5.1.1), as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent. Schedules of events are provided in Appendix A, Appendix B, Appendix C, Appendix D, and Appendix E.

Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2. Parts A and B (q3wk LV dosing)

6.2.1. Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (See Section 7.1)
- Brain CT or magnetic resonance imaging (MRI)
- Collection of archived tumor specimen, if available
- Biopsy, freshly obtained, submitted for central assessment (see Appendix E)
- Electrocardiogram (ECG) (see Section 7.1.1)
- Serology for hepatitis B surface antigen and antihepatitis B core antibody (detailed in Section 7.5.3)
- PCR for hepatitis C virus (detailed in Section 7.5.3)
- HbA1c and fasting blood glucose (detailed in Section 7.5.3)
    - If HbA1c or fasting glucose is elevated with confirmation upon repeat testing (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, or ≥7.0 mmol/L), the patient should receive glucose management before Cycle 1 Day 1 or within the first week of Cycle 1
- PT/PTT/aPTT/INR (detailed in Section 7.5.3)
- CT of chest, abdomen, and pelvis (and neck if clinically indicated) (MRI may also be acceptable; see Section 7.1)Thyroid function tests (detailed in Section 7.5.3)
- Collection of concomitant medication information
- Collection of AEs

6.2.2. Baseline Visit (Days –7 to 1)

- Height and weight (see Section 7.1)
- Vital signs (see Section 7.5.2)
- Physical examination (see Section 7.5.4)
- ECOG Performance status (see Appendix F)
- Serum chemistry panel (detailed in Section 7.5.3)
- Complete blood count (CBC) with differential (detailed in Section 7.5.3)

- Pregnancy test for patients of childbearing potential – performed within 3 days prior to Cycle 1 Day 1 (performed locally)
- Collection of concomitant medication information
- Collection of AEs

6.2.3. Treatment Period (Day 1 to Day 21)

6.2.3.1. Day 1

For Cycle 1, if baseline visit activities occur within 1 day prior to Day 1, the following assessments do not need to be repeated. For Cycle 2 and beyond, these assessments have a window of -2 days:

- Physical examination (see Section 7.5.4)
- Weight
- ECOG performance status (see Appendix F)
- Serum chemistry panel (detailed in Section 7.5.3) **to be evaluated prior to infusion.** Hold dose if blood glucose level is >250 mg/dL.
- CBC with differential (detailed in Section 7.5.3) **to be evaluated prior to infusion.**
- Pregnancy test (for patients of childbearing potential; performed locally; does not need to be repeated if performed within 3 days of Day 1)
- Thyroid function tests (detailed in Section 7.5.3; to include TSH, T3 or free T3, and free T4). Day 1 of each odd-numbered cycle only (i.e. Cycles 1, 3, 5, 7, etc.)

The following procedures must be performed on Day 1 of every cycle:

- Vital signs (within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion, within 2 hours of ending each infusion, and during infusion/s as clinically indicated (See Section 7.5.2)
- Predose blood samples for biomarkers (Cycle 1 only). See time points in Appendix E.
- Predose blood samples for PK (Cycle 1 only). See time points in Appendix B.
- Post dose blood samples for PK (Cycle 1 only). See time points in Appendix B.
- Predose blood samples for ATA (Cycle 1 only). See time points in Appendix B.
- LV infusion (if dosing criteria in Section 5.2.3.5 are met)
- Pembrolizumab infusion
- Collection of concomitant medication information
- Collection of AEs

6.2.3.2. Day 3 (Part B Cycle 1 required for patients in US sites, optional for patients outside US sites; window: Days 3–4)

- Blood samples for PK

6.2.3.3. Day 5 (Part A Cycle 1 only; window: Days 4–7)

- Fresh tumor biopsy

- Blood samples for PK
- Blood samples for biomarkers
- Collection of concomitant medication information
- Collection of AEs

6.2.3.4. Day 8 (Cycles 1-2 only; ±2 days)

- CBC with differential (detailed in Section 7.5.3)
- Serum chemistry panel (detailed in Section 7.5.3)
- Collection of concomitant medication information
- Collection of AEs
- Cycle 1 only:
  - Blood samples for PK

6.2.3.5. Day 15 (Cycle 1 only; ±2 days)

- Fresh tumor biopsy only for patients enrolled in Part B (window: Days 15–21)
- Blood samples for PK
- Collection of concomitant medication information
- Collection of AEs

6.3. Parts C (q1wk LV dosing) and D (Days 1 and 8 LV dosing)

6.3.1. Screening Visit (Day –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (See Section 7.1)
- Brain CT or MRI
- Biopsy, archival or freshly obtained, submitted for the following:
  - Central assessment of exploratory biomarker assessments (see Appendix E)
  - Part D only: Local laboratory determination of PD-L1 CPS <10 by a PD-L1 IHC assay using the 22C3 clone (see Section 7.1)
- ECG (see Section 7.1.1)
- Serology for hepatitis B surface antigen and antihepatitis B core antibody (detailed in Section 7.5.3)
- PCR for hepatitis C virus (detailed in Section 7.5.3)
- HbA1c and fasting blood glucose (detailed in Section 7.5.3)
  - If HbA1c or fasting glucose is elevated with confirmation upon repeat testing (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, or ≥7.0 mmol/L), the patient should receive glucose management before Cycle 1 Day 1 or within the first week of Cycle 1
- PT/PTT/aPTT/INR (detailed in Section 7.5.3)
- CT of chest, abdomen, and pelvis (and neck if clinically indicated) (MRI may also be acceptable; see Section 7.1)

- Thyroid function tests (detailed in Section 7.5.3)
- Collection of concomitant medication information
- Collection of AEs

6.3.2. Baseline Visit (Day –7 to 1)

- Height and weight (see Section 7.1)
- Vital signs (see Section 7.5.2)
- Physical examination (see Section 7.5.4)
- ECOG Performance status (see Appendix F)
- Serum chemistry panel (detailed in Section 7.5.3)
- CBC with differential (detailed in Section 7.5.3)
- Pregnancy test for patients of childbearing potential – performed within 3 days prior to Cycle 1 Day 1 (performed locally)
- Collection of concomitant medication information
- Collection of AEs

6.3.3. Treatment Period (Day 1 to 21 of each cycle)

6.3.3.1. Day 1

The following assessments have a window of -2 days. If baseline visit activities occur within 2 days prior to Day 1, the assessments do not need to be repeated.

- Pre-dose
  - Physical exam
  - Weight
  - ECOG performance status (see Appendix F)
  - Serum chemistry panel (detailed in Section 7.5.3) to be evaluated prior to infusion. **Hold dose if blood glucose level is >250 mg/dL.**
  - CBC with differential (detailed in Section 7.5.3) to be evaluated prior to infusion.
  - Pregnancy test (for patients of childbearing potential; performed locally; does not need to be repeated if performed within 3 days of Day 1)
  - Thyroid function tests (detailed in Section 7.5.3; to include TSH, T3 or free T3, and free T4). Day 1 of each odd-numbered cycle only (i.e. Cycles 1, 3, 5, 7, etc.)

The following procedures must be performed on Day 1:

- Vital signs (within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion, within 2 hours of ending each infusion, and during infusion/s as clinically indicated (See Section 7.5.2)
- Predose blood samples for biomarkers (Cycle 1 only). See time points in Appendix D.
- Predose blood samples for PK (Cycle 1 only). See time points in Appendix D.
- Post dose blood samples for PK (Cycle 1 only). See time points in Appendix D.
- Predose blood samples for ATA (Cycle 1 only). See time points in Appendix D.
- LV infusion (if dosing criteria in Section 5.2.3.5 are met)
- Pembrolizumab infusion
- Collection of concomitant medication information
- Collection of AEs

6.3.3.2. Day 3 (Cycle 1 only; required for patients in US sites, optional for patients outside US sites; window: Days 3–4)

- Blood samples for PK

6.3.3.3. Day 8

- Pre-dose
  - Serum chemistry panel (detailed in Section 7.5.3) **to be evaluated prior to infusion** (Cycles 1 and 2 only).
  - CBC with differential (-2-day window; detailed in Section 7.5.3) **to be evaluated prior to infusion.**
  - Blood samples for PK assessment (Cycle 1 only; see Appendix D)
- Vital signs (within 60 minutes prior to LV infusion, within 2 hours of ending of infusion, and during infusion as clinically indicated. See Section 7.5.2)
- LV infusion
- Post-dose
  - Cycle 1 only: blood samples for PK assessment (Appendix D)

6.3.3.4. Day 15

Part C

- Pre-dose
  - Serum chemistry panel (detailed in Section 7.5.3) **to be evaluated prior to infusion** (Cycles 1 and 2 only).
  - CBC with differential (-2-day window; detailed in Section 7.5.3) **to be evaluated prior to infusion.**
  - Blood samples for PK assessment (Cycle 1 only; see Appendix D)
- Vital signs (within 60 minutes prior to LV infusion, within 2 hours of ending of infusion, and during infusion as clinically indicated. See Section 7.5.2)
- LV infusion (if dosing criteria in Section 5.2.3.5 are met)

- Post-dose
  - Cycle 1 only: blood samples for PK assessment (Appendix D)

Part D

- CBC with differential (-2-day window; detailed in Section 7.5.3 (Cycles 1 and 2 only).

6.4. Response Assessments

Time points for radiographic exams should be calendar based and do not depend on cycle visits (see Section 7.2). Imaging should be conducted on the following schedule until disease progression, unacceptable toxicity, start of a new cancer therapy, consent withdrawal, investigator decision, study termination by the sponsor, or death, whichever comes first:

Every 6 weeks (±3 days) for 12 months after the first dose of LV and pembrolizumab

Every 12 weeks (±7 days) thereafter

No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time.

6.5. End of Treatment Visit (30 to 37 days after last dose of study drug)

End of treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for AEs.

- ECOG Performance status (see Appendix F)
- Physical examination (see Section 7.5.4)
- Pregnancy test (for patients of childbearing potential; performed locally)
- Serum chemistry panel (detailed in Section 7.5.3)
- CBC with differential (detailed in Section 7.5.3)
- HbA1c (performed locally)
- CT of chest, abdomen, and pelvis (and neck if clinically indicated) (MRI may also be acceptable; see Section 7.1) (not required if conducted within 4 weeks prior to EOT)
- Collection of concomitant medication information
- Collection of AEs

If patients are discontinuing treatment due to PD, and a biopsy was done as standard of care at disease progression, a tumor sample is requested, if available.

6.6. Follow-up

Patients who discontinue study treatment in the absence of disease progression will remain on the study for follow-up until withdrawal of consent, initiation of a new anticancer therapy, death, or study closure, whichever occurs first.

The first follow-up visit will occur 6 weeks (±1 week) from the most recent prior radiographic response evaluation. Subsequent follow-up visits will be scheduled for 6 weeks (±1 week) from the previous follow-up visit. After 1 year on study, the frequency of follow-up visits will be reduced to every 12 weeks (±1 week).

The following assessments will be conducted at follow-up visits until progression or initiation of a new anticancer treatment through the end of the safety follow-up period:

- Physical examination (see Section 7.5.4)
- CT of chest, abdomen, and pelvis (and neck if clinically indicated) (MRI may also be acceptable; see Section 7.1); after a year of follow-up, reduce frequency to institution's standard of care until progression or initiation of a new anticancer therapy.
- Concomitant medication information and AEs to be collected if serious and considered to be study treatment-related.

Safety Follow-Up

Patients discontinuing treatment will be followed for the protocol required safety follow-up period, unless additional safety concerns warrant further follow-up:

- 30 days post treatment for LV and
- 90 days post treatment for pembrolizumab.

No additional follow-up is required after the safety follow-up period.

After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted, every 12 weeks (±2 weeks) starting from the last radiographic scan demonstrating disease progression or from initiation of the new anticancer treatment until completion of the safety follow-up period, death, or study closure, whichever comes first. Follow-up may be conducted with clinic visits or telephone calls. No further response assessments will be conducted.

6.7. End of Study/End of Follow-up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded.

The study will be closed when no patients remain in follow-up.

For patients still receiving treatment or in the safety follow-up period, the investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.5.1.2 and Section 7.5.1.4 for each patient.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

- Patient medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.
- Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult patients only, measurements of height obtained within the prior 12 months may be utilized.
- Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Clinical laboratory tests including PT/PTT/aPTT/INR, HbA1c, serology for hepatitis B, PCR for hepatitis C, pregnancy test (either urine or serum, for patients of childbearing potential), and thyroid function tests (to include TSH, T3 or free T3, and free T4) are required for all patients at screening. Clinical laboratory tests are further detailed in Section 7.5.3.

A brain scan (CT with contrast/MRI scan) for baseline tumor imaging should be performed to assess disease at baseline.

For patients enrolled in Part D, available and adequate archival or fresh baseline tumor biopsy tissue is required (see Section 7.4.1 for details). The medical monitor should be contacted to consider alternatives in the event a tumor sample is not available. Tumor tissue PD-L1 CPS <10 will be determined by a PD-L1 IHC assay using the 22C3 clone.

7.1.1. Electrocardiogram

ECGs are to be obtained per institutional standard at time points defined in Section 6, Appendix A, and Appendix C.

7.2. Response/Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluation every 6 weeks (±3 days) for 12 months after the first dose of LV and pembrolizumab and every 12 weeks (±7 days) thereafter and should be calculated from Cycle 1 Day 1 during treatment. Time points for radiographic examinations should be calendar based and do not depend on cycle visits. The schedule of response assessments should not be adjusted for dose delays, dose interruptions, or other reasons for changes in the timing of a patient's study activities. No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time.

Spiral CT scans of chest, abdomen, and pelvis must be obtained; a CT of the neck must also be obtained if documented or suspected involvement in this region. A diagnostic quality CT is

required unless medically contraindicated. For patients unable to tolerate contrast-enhanced CT assessments, MRI imaging is acceptable. **Patients must be evaluated with same imaging modality throughout the study for efficacy assessments.** If any other radiographic or disease assessment examination is conducted per standard of care, the assessment information will be collected in the CRF.

The determination of antitumor activity will be based on objective response assessments made according to RECIST Version 1.1 (for primary and secondary endpoints) and iRECIST (for exploratory endpoints). Treatment decisions by the investigator will be based on iRECIST.

Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T cell response (termed pseudoprogression) with pembrolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. The iRECIST allow for continued treatment beyond apparent progression of disease in order to confirm response. In patients who have initial evidence of radiological PD per RECIST v1.1, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, patients should not discontinue treatment until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Patients' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.3. Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ATA assessment for Parts A and B will be collected at time points described in Appendix B. PK and ATA sampling time points for Parts C and D are described in Appendix D. Starting with amendment 11, PK and immunogenicity assessments will not be conducted after Cycle 1.

Sensitive, qualified ELISA or LC/MSMS assays, as appropriate, will be used to measure concentrations of ADC (LV), total antibody, and MMAE in plasma and ATA in serum. PK

parameters will be estimated for ADC, total antibody, and MMAE. Related analytes of LV may also be measured using appropriate assays.

7.4. Biomarker Studies

Tumor samples and blood for exploratory biomarkers analyses may be collected at protocol-specified time points (see Appendix E). Biomarker assessments will not be used for patient selection. Starting with Amendment 11, biomarker assessments will not be conducted after Cycle 1.

Methods of analysis may include IHC, multiplex immune histofluorescence (mIHF), mutation and gene expression profiling by Next Generation Sequencing, flow cytometry, ELISA, and T cell receptor beta (TCRβ) immunoSEQ analysis.

7.4.1. Biomarkers in Solid Tumor Tissue

To better understand relationships between pre-treatment biological characteristics of the tumor and BC patient outcomes, a freshly obtained pretreatment tumor biopsy is required for patients in Parts A and B with accessible tumors (for instructions see Laboratory Manual).

For patients in Parts A and B with inaccessible tumors or other safety concerns, archival tissue may be submitted if it was collected after completion of the patient's most recent cytotoxic therapy.

For patients in Parts C and D, archival tissue collected after completion of the patients most recent cytotoxic therapy should be submitted. If archival tissue is not available, a freshly obtained pretreatment tumor biopsy with accessible tumors can be used (for instructions see Laboratory Manual). If neither fresh nor adequate archived tissue is available, please discuss this requirement with the medical monitor.

For freshly obtained tumor biopsies, core needle or excisional biopsy is preferred. If neither is possible, discuss with medical monitor whether biopsy obtained via alternative methods may be appropriate.

For archival tissue, formalin fixed paraffin embedded (FFPE) blocks are requested. If no block is available, slides may be submitted with medical monitor approval.

Studies of CPIs in patients with several different solid cancers have shown a positive association of pretreatment tumor-infiltrating lymphocytes (TILs) as well as PD-L1 expression with improved outcomes (Rosenberg 2016; Schmid 2017). In turn, TILs and PD-L1 expression are elevated following monotherapy with MMAE-linked ADCs according to preclinical data (Cao 2017). This suggests that a combination of LV and CPI treatment could be synergistic. In addition, efficacy of CPIs is dependent on mutational load of tumors, while a combination of CPIs with LV may be independent of mutational load, and thus be efficacious in a larger patient population than CPI monotherapy.

To characterize and correlate predictive and prognostic pre-treatment biomarkers and treatment-associated changes in the tumor immune microenvironment with patient outcome, an on-treatment biopsy is required between Days 4 to 7 of Cycle 1 for patients with accessible tumors

in Part A of the study. For patients with accessible tumors in Part B, an on-treatment biopsy is required between Days 15 and 21 of Cycle 1. Two cores should be obtained. Core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate. The on-treatment biopsy should be obtained from the same lesion as the pre-treatment (or archival) biopsy, if possible. Further instructions on biopsy collection are found in the Laboratory Manual.

No on-treatment biopsies are required for patients in Parts C or D.

To characterize and understand treatment resistance, an additional optional fresh biopsy is requested at EOT for patients in Parts A and B with accessible residual tumor, again from the same lesion as previous biopsies if possible. A fresh biopsy at EOT is not requested for patients in Parts C or D.

In US patients only, if a tumor tissue sample is obtained as part of standard of care at any time point during the study, with the patient's consent, either a part of that sample or an additional sample obtained during the same procedure may be obtained to submit to the sponsor.

Exploratory biomarker assessments in freshly obtained (or archival) pre- and on-treatment tumor tissue may include, but not be limited to:

- Expression of LIV1 and PD-L1 proteins
- Gene expression analysis (e.g., different LIV1 isoforms, PD-L1)
- Markers of disease subtype (e.g., TCGA subtypes)
- Mutational load
- Markers of the tumor immune microenvironment (e.g., CD8, FOXP3, CD68)

7.4.2. Biomarkers in Blood

Effects of LV and pembrolizumab treatment of BC patients and successful therapy may also lead to changes in liquid biomarkers, e.g., by changes in the activation state of peripheral immune cells, soluble cytokines, cell-free DNA (cfDNA), TCRβ cell pellet, and/or exosomes. To understand dynamic changes of these soluble biomarkers and their relationship to efficacy and safety, blood samples may be collected at various time points during the study. Biomarker assessments in blood samples may include, but may not be limited to:

- Abundance and phenotype of immune cell subsets
- Abundance and treatment-related changes of cytokines (such as IFNg, CXCL9, CXCL10) or other proteins (such as tumor markers CA15-3, CA27-29, or carcinoembryonic antigen [CEA])
- Abundance of circulating nucleic acids (e.g., cfDNA) or exosomes as markers of tumor response or therapy resistance
- Clonality of TCRβ by immunoSEQ analysis

Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of sample.

7.4.3. Biospecimen Repository

For patients in the US who provide additional consent, remaining de-identified unused blood and/or tissue may be retained by the sponsor and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be anonymized and retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed following study completion. Patients may withdraw permission for the retention of samples at any time.

Biospecimen repository sample collection only applies to clinical sites within the US.

7.5. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an SMC as described in Section 9.3.9.6. In addition to the SMC, an ISMC composed of physicians who are not involved in this study, as well as sponsor representatives, will periodically review cumulative safety data and provide recommendations to the sponsor.

7.5.1. Adverse Events

7.5.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- All study protocol-related AEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 through the end of the safety reporting period (see Section 6). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.

- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event. (see Section 7.5.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (LV, pembrolizumab) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.5.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For IRRs, record the NCI CTCAE term of 'infusion related reaction' with an overall level of severity (per NCI CTCAE). In addition, record each sign or symptom of the reaction as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant Disease Progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

It is the responsibility of investigators or their designees to report any pregnancy or lactation (spontaneously reported to them) that occurs in a patient (or partner of a male patient) during the trial. If a patient becomes pregnant while on study, the site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the patient to be excluded from the trial.

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies and lactations that occur from the time of treatment allocation until the completion of the safety follow-up period or 30 days following the last dose of study drug(s) if the patient initiates new anticancer therapy, whichever is earlier. Include any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.5.1.1) should be reported as SAEs. Such events must be reported within 24 hours to the sponsor either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

34. Aminotransferase (ALT and/or AST) elevation >3x ULN,

AND

35. Total bilirubin >2x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

AND

36. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a suspected unexpected serious adverse reaction (SUSAR) associated with the use of the drug and reported promptly to the sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider holding study drug.

7.5.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for AEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. The reporting period for SAEs is from study Day 1 (predose) through the EOT visit or 90 days after the last study treatment, whichever is later. Events will be recorded at each examination on the Adverse Event CRFs/worksheets. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor. The investigator will make every attempt to follow all patients with non-serious AEs for outcome.

The reporting timeframe for AEs meeting any serious criteria is described in Section 7.5.1.4.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure, whichever comes first. In particular these include AEs of peripheral neuropathy in all patients.

7.5.1.4. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form).

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.5.1.5. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.5.1.4).

The sponsor will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements.

In the US, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or

condition that are anticipated to occur in the study population, should not be reported to the Food and Drug Administration (FDA) as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, the SAEs that do not require individual IND safety reports be submitted to the FDA are progression of the underlying cancer. These anticipated SAEs will be reviewed periodically by an SMC and Seagen Drug Safety Department. If upon review, an SAE is occurring at a higher rate than that which would be expected for the study population, then an IND safety report for the SAE will be submitted to the FDA.

7.5.1.6. Events of Clinical Interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECIs) and must be reported to the sponsor.

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow-up to an ECI, which occurs in any patient, must be reported within 24 hours to the sponsor if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at treatment allocation through 30 days following the last study drug dose, any ECI, or follow-up to an ECI, whether or not related to the sponsor's product, must be reported within 24 hours to the sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines.

ECIs for this trial include:

1. An overdose of either study product, as defined in Sections 5.2.4 and 5.3.4, and is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is ≥3x ULN, and an elevated total bilirubin lab value that is ≥2x ULN and, at the same time, an alkaline phosphatase lab value that is <2x ULN, as determined by way of protocol-specified laboratory testing, or unscheduled laboratory testing. *

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.5.2. Vital Signs

Vital signs include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion (Day 1 only), within 2 hours of ending each infusion, and during

infusion/s as clinically indicated. In addition, vital signs should be measured at other specified time points as outlined in the schedule of activities (see Appendix A and Appendix C).

7.5.3. Clinical Laboratory Tests

For Part A and Part B Cohort 1, samples will be drawn for central and local labs. Local laboratory testing will include blood glucose and other institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed by a central laboratory during the course of the study (schedule in Appendix A and Appendix C):

- The serum chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, blood glucose, phosphorus, potassium, sodium, total bilirubin, amylase, lipase, and uric acid.
- The CBC with differential is to include the following tests: WBC count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, absolute neutrophil count, platelet count, hemoglobin, and hematocrit.
- Tumor markers (if already being performed per the site's standard of care) such as CEA, CA15-3, and CA27-29

For Part A and Part B Cohort 1, the following laboratory assessments will be performed only by local laboratories at scheduled time points during the course of the study (see Appendix A):

- HbA1c: if HbA1c is elevated during screening, a repeat HbA1c must be obtained
- Fasting blood glucose is only required at screening (other scheduled tests do not require the patient to fast). If fasting blood glucose is elevated during screening, a repeat fasting blood glucose must be obtained.
- Coagulation parameters: PT, PTT, aPTT, and INR
- Hepatitis B virus (HBV) serology: HBsAg and HBcAb; HBV DNA test for patients with a negative HBsAg test and a positive total HBcAb.
- Hepatitis C viral load by PCR.
- Thyroid function tests, including TSH, T3 or free T3, and free T4.
- For patients of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL.

For Part B Cohort 2 and Parts C and D, all laboratory assessments will be performed locally and results are to be submitted to the central laboratory (with the exception of pregnancy testing, which does not need to be submitted to the central laboratory).

Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of samples.

7.5.4. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult patients only, measurements of height obtained within the prior 12 months may be utilized.

7.5.5. Pregnancy Testing

For women of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline, within 3 days prior to each Day 1 study drug dose at each cycle, and at the EOT visit. A negative pregnancy result is required before the patient may receive study drug. Pregnancy tests may also be repeated as requested per Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) or if required by local regulations.

7.6. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Immunogenicity is commonly assessed for biologics; therefore, standard tests may be performed to detect the possible presence of specific antibodies to LV. PK assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seagen or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current IB/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Patient coding
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seagen representative will review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seagen or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

Seagen will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3. Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities or audits by sponsor auditors.

8.4. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality (RDQ) group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the RDQ group of Seagen as part of the written record.

8.6. Data Handling and Record Keeping

8.6.1. Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the EDC system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2. Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the

period specified by Seagen, whichever is longer. The investigator must contact Seagen prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seagen.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Approximately 189-211 patients will be enrolled in this study, of which approximately 12-24 patients will be enrolled in Part A, approximately 73 patients will be enrolled in Part B (approximately 48 in Cohort 1 and approximately 25 in Cohort 2), approximately 64 patients will be enrolled in Part C, and approximately 40 patients will be enrolled in Part D.

9.1.1. Part A

Part A will start with 6 patients at 2.5 mg/kg, capped at 80 kg prior to Amendment 2 or 100 kg under Amendment 2 and later. If 2 or more patients experience a DLT, the dose level will be de-escalated to 2.0 mg/kg, capped at 80 kg prior to Amendment 2 or 100 kg for patients treated under Amendment 2 and later. If there are <2 patients experiencing DLTs, the dose level will be expanded to a total of 12 patients. If 4 or more patients experience a DLT among the 12 patients, the dose level will be de-escalated to 2.0 mg/kg, as described above. If <4 patients experience a DLT among the 12 patients, Part B Cohort 1 of the study may be initiated at 2.5 mg/kg, capped as described above.

If the dose level is reduced to 2.0 mg/kg, this dose level will initially enroll 6 patients and the same dose de-escalation algorithm will be used. If further de-escalation is needed, the dose level will be determined by the sponsor in consultation with the SMC.

If the true incidence rate of DLT is 10%, the probability of de-escalation to 2.0 mg/kg is 12%. The probability of de-escalation increases to 96% if the true incidence rate of DLT is 50%.

9.1.2. Part B

Once the MAD has been identified in Part A, patients will be enrolled in Part B Cohort 1 at the MAD. Approximately 42 LIV-1-positive patients in total will be enrolled at the MAD. Based on the SGNLVA-001 phase 1 study, it is estimated that about 70% of patients are LIV-1-positive. Approximately 60 patients are expected to be enrolled at the MAD, assuming that Part A will enroll 12 patients at the MAD and approximately 48 patients are expected to be enrolled in Part B Cohort 1 at the MAD. Assuming the observed ORR is between 50% and 70%, the widths of 2-sided 95% confidence intervals (CIs) are summarized as below.

Confirmed ORR	Expected width of 95% CI on LIV-1-positive patients (N=42)	Expected width of 95% CI on all patients at the MAD (N=60)
50%	±16%	±13%
60%	±16%	±13%
70%	±15%	±12%

Part B Cohort 2 will enroll approximately 25 patients at 2.0 mg/kg. With the patients in Part A enrolled at 2.0 mg/kg, approximately 30 patients in total will be enrolled at 2.0 mg/kg. Assuming the observed ORR is between 50% to 70%, the widths of 2-sided 95% CIs are summarized as below.

Confirmed ORR	Expected width of 95% CI on all patients at 2.0 mg/kg (N=30)
50%	±18%
60%	±18%
70%	±16%

9.1.3. Part C

In Part C, it is estimated that approximately 4 to 12 patients (assuming evaluation of 2 dose levels) will be treated in dose escalation. Operating characteristics of the dose escalation design, including the average number of patients allocated to each dose across a variety of toxicity scenarios, are presented in the simulation report (Appendix M).

Up to approximately 64 patients may be enrolled across the dose escalation and expansion cohorts in Part C (assuming 2 patients in each of the dose escalation cohort of 1.0 and 1.25 mg/kg, and 60 patients in the expansion cohort at the selected dose level of 1.25 mg/kg).

Table 9 summarizes the 2-sided 95% exact CIs among 62 patients at 1.25 mg/kg (2 in dose escalation and 60 in dose expansion cohort) assuming the observed ORR is between 50% and 70%.

Table 9: 2-sided 95% exact confidence intervals for Part C

Number of confirmed Objective Responses	Confirmed ORR(%)	95% exact CI (N=62)
31	50%	37%, 63%
37	60%	46%, 72%
43	69%	56%, 80%

9.1.4. Part D

Approximately 40 patients will be enrolled in Part D. Ongoing, real-time, continuous review of patient safety and SAEs will be conducted by the sponsor's Drug Safety Department. Additionally, the ISMC will ensure periodic safety data review throughout the study.

Presented in the table below are the 2-sided 95% exact CIs among 40 patients at 1.5 mg/kg assuming the observed ORR is between 50% and 70%.

Table 10: 2-sided 95% exact confidence intervals for Part D

Number of confirmed Objective Responses	Confirmed ORR(%)	95% exact CI (N=40)
20	50%	34%, 66%
24	60%	43%, 75%
28	70%	53%, 83%

This sample size of 40 patients would additionally provide the following probabilities of observing at least 1 patient having an AE, as summarized below.

True AE Incidence Rate	Probability of Observing at Least One Patient Having an AE (N=40)
5%	87%
10%	99%

9.2. Study Endpoint Definitions

Study endpoints are presented in Section 2. Efficacy endpoint definitions are presented in this section.

9.2.1. Objective Response Rate

The key efficacy endpoint of this study is confirmed ORR, defined as the proportion of patients with confirmed CR or PR, as determined by the investigator according to RECIST v1.1. Patients who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments, as described in Section 7.2 of the protocol, will be counted as non-responders. Exploratory analysis of objective response will be based on iRECIST.

9.2.2. Duration of Response

DOR is defined as the time from start of the first documentation of objective response (CR or PR that is subsequently confirmed), to the first documentation of disease progression (per RECIST v1.1 or per investigator claim of clinical progression), or to death due to any cause, whichever comes first.

DOR data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of the last disease assessment documenting absence of PD.
- Patients who have started a new antitumor treatment prior to documentation of PD will be censored at the date of the last disease assessment prior to the start of a new therapy. Note: Palliative radiotherapy on a non-target lesion that is not progressing will not be

considered a subsequent anticancer therapy; however, radiotherapy on any target lesion will be considered subsequent anticancer therapy.

- Patients who are removed from the study prior to documentation of PD will be censored at the date of the last disease assessment documenting the absence of PD.

DOR will only be calculated for patients achieving a confirmed CR or PR.

Analysis of DOR will also be performed based on iRECIST guidelines, with iDOR defined as the time from first documentation of objective response (that is subsequently confirmed) per investigator to the first documentation of objective disease progression (that is subsequently confirmed), or to death due to any cause, whichever comes first. Disease progression is considered to be confirmed without the confirmation scan if patient has clinical progression or becomes clinically unstable.

9.2.3. Disease Control Rate

The DCR is defined as the proportion of patients with CR, PR, or SD according to RECIST v1.1. Patients who do not have post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders.

Analysis of DCR will also be performed based on iRECIST guidelines, with iDCR defined as iCR + iPR + iSD.

9.2.4. Progression-Free Survival

PFS is defined as the time from start of study treatment to first documentation of objective progression of disease (PD per RECIST v1.1 or per investigator claim of clinical progression), or to death due to any cause, whichever comes first. For patients who are enrolled but fail to receive study treatment, the enrollment date will be used as the starting point in the calculation of PFS.

The same censoring rules outlined in Section 9.2.2 for DOR will be applied to PFS. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at Day 1.

Analysis of PFS will also be performed based on iRECIST guidelines, with iPFS defined as the time from start of study treatment to the first documentation of objective disease progression (that is subsequently confirmed). The date of progression is the first date at which progression criteria are met (i.e., the date of unconfirmed progressive disease [iUPD]), provided that confirmed progressive disease (iCPD) is established at the next assessment. Disease progression is considered to be confirmed without the confirmation scan if patient has clinical progression or becomes clinically unstable.

9.2.5. Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of death, survival time will be censored at the last date the patient is known to be alive. For patients who enroll but fail to receive study treatment, the enrollment dates will be used as the starting points in the calculation of OS.

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1. General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

9.3.1.1. Randomization and Blinding

This is a single arm, open-label study. Blinding will not be performed.

9.3.1.2. Adjustments for Covariates

Adjustments for covariates are not planned.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE dates while calculating duration of events and treatment-emergent status; details will be provided in the SAP. For time-related endpoints, e.g., PFS, patients who have no specified event will be censored at the time of the last valid assessment of the endpoint(s).

9.3.1.4. Multicenter Studies

There are multiple centers in this study; however, it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

9.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (e.g., start date and end date) will be calculated as (end date – start date + 1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of LV unless otherwise specified in the analysis plan.

9.3.1.7. Analysis Sets

The all treated analysis set includes all patients who receive any amount of LV or pembrolizumab. The all treated analysis set will be used as the primary dataset for efficacy analysis.

The safety analysis set includes all patients who receive any amount of LV or pembrolizumab. The safety analysis set will be used for all safety and PK analyses. This is also called the all treated patients set for efficacy analyses.

The efficacy-evaluable (EE) analysis set includes all patients in the all treated analysis set who had both a baseline and at least one post-baseline disease assessment according to the RECIST v1.1 and iRECIST criteria when applicable, or who had clinical disease progression per investigator.

The DLT-evaluable (DE) analysis set includes all treated patients in Part A who either (1) experienced a DLT or (2) received at least 75% of intended LV and pembrolizumab doses and were followed for the full DLT evaluation period. Patients will be replaced for DLT evaluation if, for reasons other than DLT, they are ineligible for DLT evaluation (e.g., pembrolizumab IRR Grade ≥3, receipt of prohibited concomitant medication, they do not meet eligibility criteria), or they do not complete the DLT evaluation period.

9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include, but are not limited to, the following:

- Age
- Metastatic sites
- LIV1 expression
- Disease subtype

9.3.2. Timing of Analyses

The primary analysis will be conducted when all treated patients have come off study. Subsequent cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

9.3.3. Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.4. Patient Characteristics

Demographics and other baseline characteristics will be summarized.

9.3.5. Treatment Compliance

The dose administered at each cycle for each treatment agent will be assessed and dose intensity will be summarized.

9.3.6. Efficacy Analyses

The primary analysis of efficacy endpoints will be based on the all treated analysis set. Additional analysis of efficacy endpoints will be performed using the EE analysis set as appropriate.

9.3.6.1. Primary Efficacy Analyses

The primary efficacy endpoint is the confirmed ORR per investigator assessment. The ORR is defined as the proportion of patients with confirmed CR or PR according to RECIST v1.1. Patients who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders. The observed ORR and its corresponding exact 2-sided 95% CI will be summarized using the Clopper-Pearson method (Clopper 1934).

9.3.6.2. Secondary Efficacy Analyses

The DCR per RECIST v1.1 will be summarized, and its exact 2-sided 95% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

DOR, PFS per RECIST v1.1, and OS will be estimated using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians and 95% CIs may be calculated, as appropriate.

9.3.6.3. Additional Efficacy Analyses

The ORR and DCR per iRECIST will be summarized, and their exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.

DOR and PFS per iRECIST will be estimated using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians and 95% CIs may be calculated, as appropriate.

9.3.7. Pharmacokinetic and Immunogenicity Analyses

Total Antibody drug-conjugate (LV) and unconjugated drug (MMAE) concentrations will be summarized with descriptive statistics at each PK sampling time point using the safety analysis set. Selected PK parameters for ADC (LV) and MMAE will be estimated. Data may be combined with PK data from other clinical trials with LV for population PK analyses.

The incidence of ATA will be summarized using the safety analysis set.

9.3.8. Biomarker Analyses

Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized.

9.3.9. Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

9.3.9.1. Extent of Exposure

Duration of treatment, number of cycles, total dose, and dose intensity will be summarized. Dose modifications will also be summarized.

9.3.9.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 patient, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.9.3. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4. Clinical Laboratory Results

Laboratory values (e.g., chemistry, hematology, and pulmonary function tests) may be presented graphically by visit. Summary statistics may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

9.3.9.5. Other Safety Analyses

Vital Signs

Vital signs (respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature) will be listed for each vital sign by scheduled visit. Summary statistics and change from baseline and/or predose to postdose may be tabulated where appropriate.

ECOG Status

ECOG status will be summarized for Baseline/Day 1 and EOT. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG and shifts from baseline may be tabulated.

9.3.9.6. Interim Analyses

No formal interim analyses are planned. An SMC will periodically monitor the trial for safety. The SMC will review expedited SAEs as they are received. Further details will be provided in the SMC Charter. In addition to the SMC, an ISMC composed of physicians who are not involved in this study, as well as sponsor representatives, will periodically review cumulative safety data and provide recommendations to the sponsor. Further details will be provided in the

ISMC Charter. Interim data from the study may be presented at scientific meetings such as the annual meeting of the ASCO.

Continuous monitoring of the benefit-risk profile will be conducted and continuation of enrollment to the cohort may be altered depending on the benefit-risk profile.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 [R2]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil, 2015), and all applicable regulatory requirements.

10.1. Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the patient in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient if they are able, or from a LAR, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a LAR representative for a patient who is unable to provide informed consent at study entry (if applicable), but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2. Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical IB and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4. Study Documentation, Privacy, and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS (Q3WK LV DOSING; PARTS A AND B)

Visit Window		Baseline/Screening		Enrollment	21-day Cycle				EOT	Follow-up
					D1	D5	D8	D15		
		D –28 to 1	D –7 to 1	D –7 to 1	See footnotes for window	D 4–7	±2d	±2d	30–37 days post last dose	Every 6 weeks ± 1 week[B] (unless otherwise stated)
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor prior to study start						
	Inclusion/exclusion	X								
	Medical history	X								
	Physical Exam		X		X[A,R]				X	X
	Height (baseline only) and Weight		X		X[A,R]					
	Vital signs[C]		X		X					
	Brain CT or MRI	X								
	Initiate collection of archived tumor specimen (if available)[O]	X								
	Freshly obtained biopsy[D,O] (see also Appendix E)	X				X[E]		X[E]	X[F]	
	ECG	X								
	Pregnancy test (performed locally) (patients of childbearing potential only)		X[G]		X[G]				X	
	ECOG performance status		X		X[A,R]				X	
	Hepatitis B and C screening[S]	X								
	CBC with differential[O]		X		X[A,R]		X[Q]		X	
	PT/PTT/aPTT/INR	X								
	HbA1c[I,S]	X							X	
	Fasting blood glucose[H,S]	X								
	Serum chemistry panel[O,S]		X		X[A,I,R]		X[Q]		X	
	Thyroid function tests[I,S]	X			On Day 1[R] of each odd-numbered cycle while on treatment (e.g., Day 1 of Cycles 1, 3, 5, 7, etc)					
	Concomitant medications & AEs	Collect any related to study protocol procedures that result in exclusion from the trial or study termination			Collect from Day 1 (predose) through 30 days (AEs) or 90 days (SAEs) post last dose or through EOT visit, whichever is later[B,K]					X[B,K]
Treatment	LV				X[M]					
	Pembrolizumab				X					
PK/ATA	Samples for PK				Cycle 1 Only: See PK/ATA/Biomarker Tables (Appendix B and Appendix E)					
	Samples for ATA									
	Blood sample for biomarker analysis									
Response Assessments[N]	CT or MRI of chest, abdomen, pelvis (and neck if clinically indicated)	X			Assessments to be performed every 6 weeks (±3 days) for the first 12 months and every 12 weeks (±7 days) thereafter, regardless of dose delays (see Section 7.2)				X[P]	X[L]
	Subsequent anticancer therapy status (may be conducted with in-clinic visit or via phone calls)									X

	Survival status (may be conducted with in-clinic visit or via phone calls)									X

A For Cycle 1 only, if baseline visit activities occur within 1 day prior to Day 1, these assessments do not need to be repeated.

B For patients who discontinue study treatment in the absence of disease progression, perform every 6 weeks (±1 week) until progression or initiation of a new anticancer therapy. After 1 year on study, reduce frequency to every 12 weeks (±1 week). All patients, including those with progressive disease, will be followed for survival until completion of the safety follow-up period, death or study closure, whichever occurs first every 12 weeks (±1 week) unless otherwise stated.

C Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while patient is in a seated position, pulse oximetry, and temperature. Obtain within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion, and within 2 hours of ending each infusion, and during infusion/s as clinically indicated.

D Patients with accessible tumors only. Core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate.

E Biopsy collected during Cycle 1 only. Patients in Part A with accessible tumors are required to have a biopsy between Days 4 and 7. Patients in Part B with accessible tumors are required to have a biopsy between Days 15 and 21.

F An additional optional biopsy is requested (with separate consent) at EOT for patients with accessible residual tumor from the same lesion as previous biopsies, if possible. In addition, in US patients only, if a tumor tissue sample is obtained as part of standard of care at any time point during the study, with the patient's consent, either a part of that sample or an additional sample obtained during the same procedure is requested to be submitted to the sponsor. Biomarker assessments will only be collected during Cycle 1 as of protocol Amendment 11.

G Pregnancy test must be performed within 3 days prior to each study drug dose.

H If HbA1c or fasting blood glucose is elevated during screening, a repeat HbA1c or fasting blood glucose must be obtained.

I Blood glucose sample should be obtained before administration of study drugs or any glucose-containing fluid. Hold dose if blood glucose level is >250 mg/dL or >13.9 mmol/L, testing may be repeated on same day of dosing. If HbA1c or fasting glucose are elevated (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL or ≥7.0 mmol/L) upon repeat testing, patient should receive glucose management prior to or within one week of starting study treatment.

J Thyroid function tests include TSH, T3 or free T3, and free T4.

K To be collected if serious and considered to be study treatment-related.

L For patients who discontinue study treatment, perform every 6 weeks (±1 week) during the first year, then reduce frequency per institution's standard of care until progression or initiation of a new anticancer therapy unless otherwise stated.

M For patients receiving >200 mg LV per infusion (weight >80 kg), prophylactic G-CSF administration is required and will be given to patients on the day after study treatment is given, with a visit window of Day 2-4. If pegfilgrastim is used, a one-time dose is recommended. If daily growth factor support is used, treat for at least 5-7 days or until the absolute neutrophil count is >1000/mm^3 (≤ Grade 2). Hold dose if dosing criteria outlined in Section 5.2.3.5 are not met.

N Timing of response assessments should be calculated from Cycle 1 Day 1.

O Refer to the laboratory manual for information on collection, processing, storage, and shipment of sample.

P Not required if conducted within 4 weeks prior to EOT.

Q Cycles 1-2 only

R For Cycle 2 and beyond, may be performed up to 2 days prior to Day 1.

S For Part A and Part B Cohort 1, laboratory assessments are to be performed locally and centrally. For Part B Cohort 2, laboratory assessments are to be performed locally and results are to be submitted to the central laboratory (with the exception of pregnancy testing); detailed in Section 7.5.3.

T Follow-up will occur every 6 weeks (±1 weeks) 30 days post last treatment for patients on LV only and 90 days for those on pembrolizumab.

APPENDIX B: PK AND ATA SAMPLING TIME POINTS (Q3WK LV DOSING; PARTS A AND B)

Cycle[C]	Study Day	Time	Window	Relative Time	LV PK	Pembrolizumab PK	LV ATA	Pembrolizumab ATA
Cycle 1	Day 1	Predose of LV	Within 8 hrs	START of LV infusion	X	X	X	X
		End of LV infusion	Within 30 min	END of LV infusion	X			
		End of pembrolizumab infusion	Within 30 min	END of pembrolizumab infusion		X		
	Day 3[B]	48 hrs	Day 3-4	START of LV infusion	X	X		
	Day 5[A]	96 hrs	Day 4–7	START of LV infusion	X	X		
	Day 8	168 hrs	±48 hrs	START of LV infusion	X	X		
	Day 15	336 hrs	±48 hrs	START of LV infusion	X	X		
Cycles 2 and 4	Day 1	Predose of LV	Within 8 hrs	START of LV infusion	X	X	X	X
		End of LV infusion	Within 30 min	END of LV infusion	X			
		End of pembrolizumab infusion	Within 30 min	END of pembrolizumab infusion		X		
Cycles 3, 5, and every 5 cycles thereafter (e.g., Cycles 10, 15)	Day 1	Predose of LV infusion	Within 8 hrs	START of LV infusion	X	X	X	X
EOT					X	X	X	X

A Day 5 assessments to be performed for patients in Part A only.
B Day 3 assessments (Part B Cycle 1 only) required for US patients, optional for EX-US patients. Requires separate informed consent for EX-US patients.
C Biomarker assessments will only be collected during Cycle 1 as of protocol Amendment 11.

APPENDIX C: SCHEDULE OF EVENTS (PARTS C AND D)

Visit Window		Baseline/Screening		Enrollment	21-day Cycle			EOT	Follow-up
					D1	D8	D15		
		D –28 to 1	D –7 to 1	D –7 to 1	See footnotes for window	See footnotes for window	See footnotes for window	30–37 days post last dose	Every 6 weeks ±1 week[B,V]
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor prior to study start					
	Inclusion/exclusion	X							
	Medical history	X							
	Physical Exam		X		X[A,Q]			X	X
	Height (baseline only) and Weight		X		X[A,Q]				
	Vital signs[C]		X		X	X	X[U]		
	Brain CT or MRI	X							
	Initiate collection of archived tumor specimen (if available)[N,V]	X							
	Freshly obtained biopsy[D,M,T] (see also Appendix E)	X							
	ECG	X							
	Pregnancy test (performed locally) (patients of childbearing potential only)		X[E]		X[E]			X	
	ECOG performance status		X		X[A,P]			X	
	Hepatitis B and C screening[Q]	X							
	CBC with differential[M,Q]		X		X[A,Q]	X	X[U]	X	
	PT/PTT/aPTT/INR[Q]	X							
	HbA1c[G,Q]	X						X	
	Fasting blood glucose[F,Q]	X							
	Serum chemistry panel[M,Q]		X		X[A,G,Q]	X[G,R]	X[G,R,S]	X	
	Thyroid function tests[H,Q]	X			On Day 1[S] of each odd-numbered cycle while on treatment (e.g., Day 1 of Cycles 1, 3, 5, 7, etc)				
	Concomitant medications & AEs	Collect any related to study protocol procedures that result in exclusion from the trial or study termination			Collect from Day 1 (predose) through 30 days (AEs) or 90 days (SAEs) post last dose or through EOT visit, whichever is later[B,I]				X[U]
Treatment[K]	LV[K,O,P]				X	X	X[S]		
	Pembrolizumab				X				
PK/ATA	Samples for PK				Cycle 1 Only: See PK/ATA/Biomarker Tables (Appendix D and Appendix E)				
	Samples for ATA								
	Blood sample for biomarker analysis								
Response Assessments[L]	CT or MRI of chest, abdomen, pelvis (and neck if clinically indicated)[S]	X			Assessments to be performed every 6 weeks (±3 days) for the first 12 months and every 12 weeks (±7 days) thereafter, regardless of dose delays (see Section 7.2)			X[N]	X[J]
	Subsequent anticancer therapy status (may be conducted with in-clinic visit or via phone calls)								X

	Survival status (may be conducted with in-clinic visit or via phone calls)								X

A For Cycle 1 only, if baseline visit activities occur within 2 days prior to Day 1, these assessments do not need to be repeated.
B For patients who discontinue study treatment in the absence of disease progression, perform every 6 weeks (±1 week) until progression or initiation of a new anticancer therapy. After 1 year on study, reduce frequency to every 12 weeks (±1 weeks). All patients, including those with progressive disease, will be followed for survival until completion of the safety follow-up period, death, or study closure, whichever occurs first unless stated otherwise.
C Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while patient is in a seated position, pulse oximetry, and temperature. Obtain within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion (Day 1 only), and within 2 hours of ending each infusion, and during infusion/s as clinically indicated.
D If archived tumor specimen is not collected and for patients with accessible tumors only. Core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate.
E Pregnancy test must be performed within 3 days prior to each Day 1 study drug dose.
F If HbA1c or fasting blood glucose is elevated during screening, a repeat HbA1c or fasting blood glucose must be obtained.
G Blood glucose sample should be obtained before administration of study drugs or any glucose-containing fluid. Hold dose if blood glucose level is >250 mg/dL or >13.9 mmol/L, testing may be repeated on same day of dosing. If HbA1c or fasting glucose are elevated (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL or ≥7.0 mmol/L) upon repeat testing, patient should receive glucose management prior to or within one week of starting study treatment.
H Thyroid function tests include TSH, T3 or free T3, and free T4.
I To be collected if serious and considered to be study treatment-related.
J For patients who discontinue study treatment in the absence of disease progression, perform every 6 weeks (±1 week) during the first year, then reduce frequency per institution's standard of care until progression or initiation of a new anticancer therapy unless otherwise stated.
K The maximum dose is 200 mg per infusion.
L Timing of response assessments should be calculated from Cycle 1 Day 1.
M Refer to the laboratory manual for information on collection, processing, storage, and shipment of sample.
N Not required if conducted within 4 weeks prior to EOT.
O At least 7 days must elapse between administrations of LV. Hold dose if dosing criteria outline in Section 5.2.3.5 are not met.
P For Cycle 2 and beyond, may be performed up to 2 days prior to Day 1.
Q Laboratory assessments are to be performed locally and results are to be submitted to the central laboratory (with the exception of pregnancy testing); detailed in Section 7.5.3.
R Cycles 1 and 2 only.
S Part C only.
T In Part D only, archival or freshly obtained tumor tissue will be used to determine eligibility based on PD-L1 CPS<10 status as determined locally by a PD-L1 IHC assay using the 22C3 clone.
U Cycles 1 and 2 only for Part D and every cycle for Part C.
V Follow-up will occur every 6 weeks (±1 weeks) 30 days post last treatment for patients on LV only and 90 days for those on pembrolizumab.

APPENDIX D: PK AND ATA SAMPLING TIME POINTS (PARTS C AND D)

Cycle	Study Day	Time[C]	Window	Relative Time	LV PK	Pembrolizumab PK	LV ATA	Pembrolizumab ATA
Cycle 1	Day 1	Predose of LV	Within 8 hrs	START of LV infusion	X	X	X	X
		End of LV infusion	Within 30 min	END of LV infusion	X			
		End of pembrolizumab infusion	Within 30 min	END of pembrolizumab infusion		X		
	Day 3[A]	48 hrs	Day 3-4	START of Day 1 LV infusion	X			
	Day 8	Pre-dose of LV	Within 8 hrs	START of LV infusion	X			
		End of LV infusion	Within 30 min	END of LV infusion	X			
	Day 15[B]	Pre-dose of LV	Within 8 hrs	START of LV infusion	X			
		End of LV infusion	Within 30 min	END of LV infusion	X			
Cycles 2 and 4	Day 1	Predose of LV	Within 8 hrs	START of LV infusion	X	X	X	X
		End of LV infusion	Within 30 min	END of LV infusion	X			
Cycles 3, 5, and every 5 cycles thereafter (e.g., Cycles 10, 15)	Day 1	Predose of LV infusion	Within 8 hrs	START of LV infusion	X	X	X	X
EOT					X	X	X	X

A Day 3 assessments required for US patients, optional for EX-US patients. Requires separate informed consent for EX-US patients
B Part C only.
C Biomarker assessments will only be collected during Cycle 1 as of protocol Amendment 11.

APPENDIX E: BIOMARKER SAMPLING TIME POINTS

Table 11: Biomarker sampling time points – Parts A and B*

Cycle	Study Day	Time[C]	Window	Relative Time	Cytokines	cfDNA	Exosomes	Immune subsets	TCRβ Cell Pellet	Fresh Biopsy
		N/A								
Screening	Day –28 to –1	N/A	N/A	N/A						X
Cycle 1	Day 1	Predose	Within 8 hr	START of infusion	X	X	X	X	X	
	Day 5	–	Day 4–7	START of infusion						X[A]
	Day 15	336 h	±24 hr	START of infusion						X[A]
Cycles 2, 3	Day 1	Predose	Within 8 hr	START of infusion	X	X	X	X	X	
EOT					X	X	X	X	X	X[B]

*If additional tests, including but not limited to tumor marker assessments, are performed as part of standard of care, please submit those results.
A Patients in Part A with accessible tumors are required to have a biopsy between Days 4 and 7 of Cycle 1. Patients in Part B with accessible tumors are required to have a biopsy between Days 15 and 21 of Cycle 1.
B Optional biopsy; requires separate informed consent.
C Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11.

Table 12: Biomarker sampling time points – Parts C and D*

Cycle[B]	Study Day	Time	Window	Relative Time	Cytokines	cfDNA	TCRβ Cell Pellet	Fresh Biopsy
		N/A						
Screening	Day –28 to –1	N/A	N/A	N/A				X[A]
Cycle 1, 2, and 4	Day 1	Predose	Within 8 hr	START of infusion	X	X	X	
EOT					X	X	X	

*If additional tests, including but not limited to tumor marker assessments, are performed as part of standard of care, please submit those results.
A Fresh tumor biopsy required if archival tissue is not available.
B Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11.

APPENDIX F: PERFORMANCE STATUS SCALES CONVERSION

APPENDIX G: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of the safety follow-up period.

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:

- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

APPENDIX H: P-GP AND CYP3A INDUCERS/INHIBITORS

NOTE: Additional P-gp inducers/inhibitors or strong CYP3A inducers/inhibitors may become available while the clinical trial is ongoing. The following statements would apply to those medications in addition to those listed in the table below.

Patients who are receiving P-gp or strong CYP3A inhibitors concomitantly with LV should be closely monitored for adverse reactions. Based upon evaluation of the anti-CD30 MMAE ADC brentuximab vedotin (Adcetris) (ADCETRIS Prescribing Information, Seagen, June 2023), concomitant use of P-gp inhibitors or strong CYP3A4 inhibitors has the potential to increase the exposure to MMAE (the cytotoxic component of LV and brentuximab vedotin). Concomitant use of P-gp inducers or strong CYP3A4 inducers could decrease exposure to MMAE.

P-gp Inhibitors	Strong CYP3A Inhibitors
amiodarone	boceprevir
carvedilol	clarithromycin
clarithromycin	cobicistat
dronedarone	conivaptan
itraconazole	danoprevir and ritonavir
lapatinib	diltiazem
lopinavir and ritonavir	elvitegravir and ritonavir
propafenone	grapefruit juice
quinidine	idelalisib
ritonavir	indinavir and ritonavir
ranolazine	itraconazole
saquinavir and ritonavir	ketoconazole
telaprevir	lopinavir and ritonavir
tipranavir and ritonavir	nefazodone
verapamil	nelfinavir
	paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
	posaconazole
	ritonavir
	saquinavir and ritonavir
	telaprevir
	tipranavir and ritonavir
	troleandomycin
	voriconazole
P-gp Inducers/Strong CYP3A Inducers	
avasimibe	
carbamazepine	
phenytoin	
rifampin	
St John's wort	
tipranavir and ritonavir*	

*P-gp inducer only.

APPENDIX I: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

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On-line source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX J: RECIST CRITERIA SUMMARY (VERSION 1.1)

Response Evaluation Criteria in Solid Tumors

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of 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 0.5 cm. 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.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

From RECIST Version 1.1 (Eisenhauer 2009)

A response (CR or PR) will be considered confirmed if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a patient had PR in week 8, SD in week 12, and PR in week 16, this PR will be considered as confirmed.

APPENDIX K: IRECIST: GUIDELINES FOR RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS

Response will also be assessed using iRECIST guidelines (Seymour 2017). Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST Version 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST guidelines are designated with a prefix; iRECIST time-point and best responses will be recorded separately.

Confirming Disease Progression

Unlike RECIST Version 1.1, the iRECIST guidelines require the confirmation of progression and use the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

For iCPD to be confirmed, further increase in tumor burden, compared to the last assessment, must be seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST Version 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumor burden
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST Version 1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline).

New Lesions

New lesions should be assessed and measured as they appear using RECIST Version 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected separately in the source documents.

APPENDIX L: MYELOID GROWTH FACTOR SUPPORT RECOMMENDATIONS

For patients in Parts A and B: **Primary Prophylaxis** with granulocyte-colony stimulating factor (G-CSF) starting with the first cycle of LV and continuing through subsequent cycles is recommended for patients who have approximately 20% or higher risk of febrile neutropenia. Starting with Amendment 2 for patients in Parts A and B, G-CSF is required for patients weighing >80 kg at baseline, starting with their first cycle of therapy and at each subsequent cycle. Therefore, patients weighing >80 kg must not have contraindications to myeloid growth factors and must be willing to receive them.

For patients in Part C: Primary prophylactic G-CSF is not permitted in the DLT evaluation period during dose escalation.

For patients in Part D: Primary prophylactic G-CSF may not be appropriate because LV is given either weekly or on Days 1 and 8 every 21 days.

Patients in Parts A and B who experience Grade 4 neutropenia or febrile neutropenia of any grade in any cycle, must receive myeloid growth factors in all subsequent cycles. Myeloid growth factor support is also required for treatment of febrile neutropenia in Parts A and B.

Strongly consider primary prophylaxis when allowed per protocol based on patient, disease, and treatment risk factors, including the following:

Age ≥65 years
Advanced disease
Previous chemotherapy or radiation therapy
Pre-existing neutropenia or bone marrow involvement with tumor
Infection
Open wounds or recent surgery
Poor performance status or poor nutritional status
Poor renal function
Liver dysfunction, most notably elevated bilirubin
Cardiovascular disease
Multiple comorbid conditions

Secondary prophylaxis with G-CSF is recommended for patients in Parts C and D who experience a neutropenic complication with previous cycle of therapy (for which primary prophylaxis was not received), when dose reduction or delay may compromise treatment outcome with LV.

Treatment with G-CSF is strongly recommended for patients in Part C with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include:

Sepsis syndrome (hypotension and multi-organ dysfunction)
Age >65 years
Profound neutropenia (absolute neutrophil count <0.1 x 10^9/L)
Uncontrolled primary disease
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

Refer to the Prescribing Information for the applicable G-CSF to determine the appropriate administration window for use with LV.

The choice of G-CSF is as determined by investigator.

Reference: (Crawford 2010; Smith 2015)

APPENDIX M: MODIFIED TOXICITY PROBABILITY INTERVAL DESIGN SIMULATION REPORT

Introduction

Part C of this study evaluates weekly (q1wk) LV dosing (Day 1, Day 8, and Day 15 of every 3-week cycle). The primary objective of Part C is to evaluate the safety, tolerability, and identify the recommended dose of LV. Toxicity is measured by dose-limiting toxicities (DLTs) observed within the first cycle. Dose escalation in Part C will be conducted according to a modified toxicity probability interval method (mTPI).

DOSE ESCALATION

Overview

There will be 2 selected dose levels for LV in Part C. Intermediate doses of LV may also be evaluated during the execution phase at the discretion of the sponsor upon recommendation by the Safety Monitoring Committee (SMC).

The starting dose level of LV is 1.0 mg/kg. Dose escalation is conducted according to an mTPI method and according to a set of rules governing entry into the study and assignment of dose level. Decisions are described in Section 3.1.3 of the study protocol and detailed in this appendix. They are based on the posterior distribution of the DLT rate and derived independently for each dose level. The trial is closely monitored for safety and for identification of the MTD. If the SMC recommends exploration of an intermediate dose level, an additional dose level may be added.

Modified Toxicity Probability Interval Method

Dose escalation is conducted using the modified toxicity probability interval method. The implementation programs are available at: https://udesign.laiyaconsulting.com/.

For each dose level, i, the probability of a DLT on dose i is denoted by pi. The target toxicity probability in this study is defined as 25%, with a 5% margin. The equivalence interval is [20%, 30%], which contains the doses close to the true target DLT rate that physicians would deem acceptable for treating future patients. The equivalence interval partitions the unit interval (0, 1) into 3 subintervals: (0, 20%), [20%, 30%], and (30%, 1). Doses in these 3 intervals correspond to:

1. Under dosing: pi <20%
2. Proper dosing: 20% ≤ pi ≤30%
3. Over dosing: pi >30%

In each dose level, the prior distribution of DLT probability, pi, is assumed to be non-informative Beta(1, 1). After each patient is treated and assessed for DLT, the posterior distribution of pi is updated to Beta(1 + xi, 1 + ni – xi), where xi and ni denote the number of DLTs and the number of DLT-evaluable patients at dose level i, respectively. The dose-escalation decision is based on the unit probability mass (UPM) on the posterior distribution of pi. For a given interval [a, b], the

UPM is defined as the ratio of the probability of the interval to the length of the interval, where for any DLT probability pi and
$0 \leq a < b \leq 1$,

$UPM(a, b) = Pr(a < pi < b) / (b - a)$

After the toxicity outcomes are observed, the UPM on (0, 20%), [20%, 30%], and (30%, 1) at the current dose is calculated, and the dosing decision rules are:

1. Escalate (E), if (0, 20%) has the largest UPM
2. Stay at the current dose (S), if [20%, 30%] has the largest UPM
3. De-escalate (D), if (30%, 1) has the largest UPM

In addition, the toxicity of a dose is defined as being unacceptable if there is more than a 95% probability that the DLT rate is higher than 25%,

Toxicity at dose i is unacceptable: $Pr(pi > 25\%) > 95\%$

If dose level i is determined to be unacceptable, the next patients are treated at dose level $i - 1$ and doses i and higher are excluded from the trial. If i=1, the trial is terminated, and it is concluded that no dose level is safe, if there are no lower dose levels of interest to explore. The decision rules for each dose level are provided in Table 13.

Table 13: Decision rules for SGNLVA-002 – Part C, by mTPI for each dose level with target MTD = 25%

	Number of DLT-Evaluable Patients Treated at Current Dose								
Number of Toxicities	2	3	4	5	6	7	8	9
0	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E
2	D[a]	D	D	S	S	S	S	S
3		DU	DU	DU	D	S	S	S
4			DU	DU	DU	DU	DU	D
5				DU	DU	DU	DU	DU
6					DU	DU	DU	DU
7						DU	DU	DU
8							DU	DU
9								DU

E=Escalate to the next higher dose, S=Stay at the current dose, D=De-escalate to the next lower dose, DU=Current dose is unacceptably toxic

a Dose will be de-escalated if the first 2 DLT-evaluable patients in a dose level experience DLT. Further evaluation of that dose level may be allowed if recommended by the SMC.

At the end of the trial when the toxicity outcomes of all the enrolled DLT-evaluable patients are observed, a dose will be selected as the estimated MTD. The estimation is separated from the design for dose finding. The MTD is selected by performing an isotonic regression that borrows strength across doses. Let $\hat{p}i$ be the posterior mean of DLT rate. The pooled adjacent violators algorithm (PAVA) is applied on $\hat{p}i$ so that the resulting transformed values $\hat{p}i^*$ increase with the

dose levels. That is, $\hat{p}i^* \leq \hat{p}i+1^*$ for all i. The recommended MTD is the highest dose with a toxicity probability $\hat{p}i^*$ less than or equal to the target DLT rate 25%, i.e.,

Estimated MTD = max {i: $\hat{p}i^* \leq 25\%$}

Dose-Escalation Rules

1. Dose escalation begins with patient enrollment to dose level of 1.0 mg/kg. At least 2 DLT-evaluable patients per dose level are required to escalate at any dose level. Once all patients in the previous cohort have completed DLT evaluation, patients can be enrolled to the next dose-level cohort. Subsequent enrollment and dose selection occurs via the following rules:
2. If a dose level i is unacceptable, de-escalate to the lower dose level and never treat future patients at level i. If i =1, stop the trial and conclude no dose is safe.

Interim Monitoring

The dose escalation will be closely monitored for safety and for identification of the MTD. If no doses are safe, dose escalation for that population will stop, and no MTD will be declared.

Safety Monitoring

If no doses are safe, dose escalation will stop, and no MTD will be declared. Formally, if

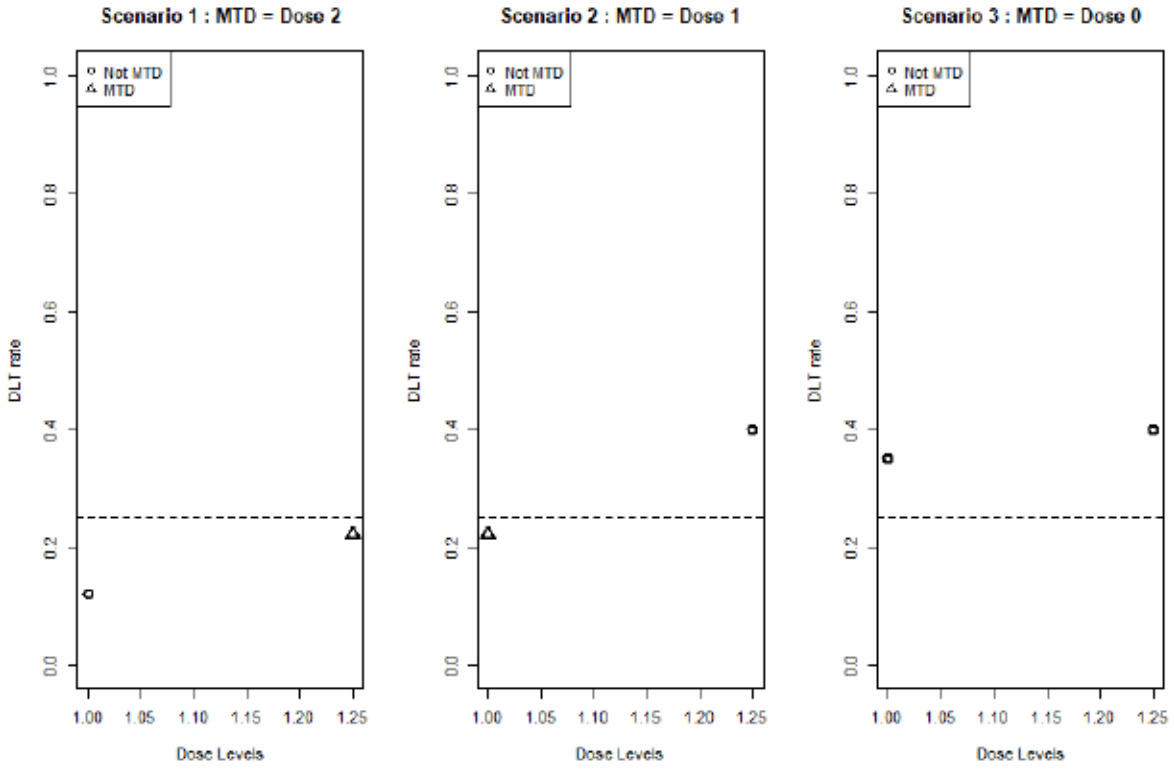
Pr(pi >25%) >95% for all i

Identification of the MTD

After each dose-level cohort, the estimation of MTD will be performed. If the model's next recommended dose is the same or below the MTD, the dose escalation may be stopped and MTD can be declared. Alternatively, if the model's next recommended dose is above the estimated MTD level, and patients have already been treated at the higher dose level, and the observed DLT rate at the recommended higher dose level exceeds the target DLT rate of 25%, the dose escalation may also be stopped and MTD can be declared.

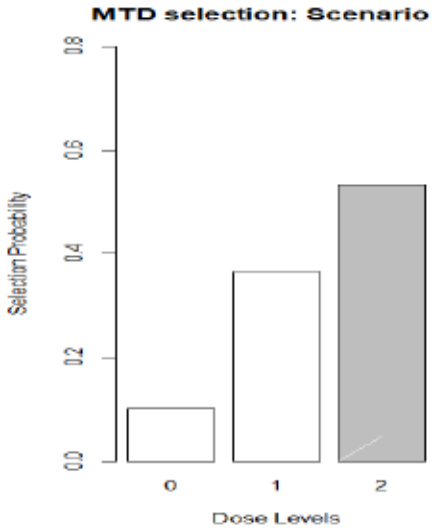
Simulation Studies

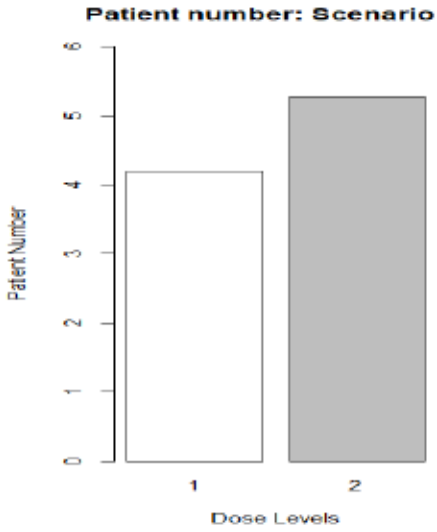
To evaluate the operating characteristics of the dose-escalation design, simulation studies were performed for the following scenarios.



The plots illustrate the true DLT rate at each dose level. For Part C simulation, dose level 1 is 1.0 mg/kg and dose level 2 is 1.25 mg/kg. For example, Scenario 1 assume that MTD is 1.25 mg/kg, Scenario 2 assume that MTD is 1.0 mg/kg, and Scenario 3 assume that no selected dose is safe.

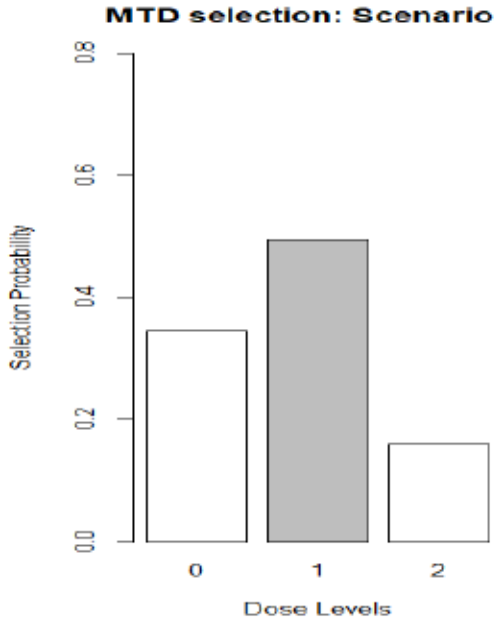
In each scenario, the dose-escalation and MTD-estimation process is replaced with 1000 replications. The probability of selecting an MTD, average number of DLT and the average number of patients treated, at each dose level is provided.

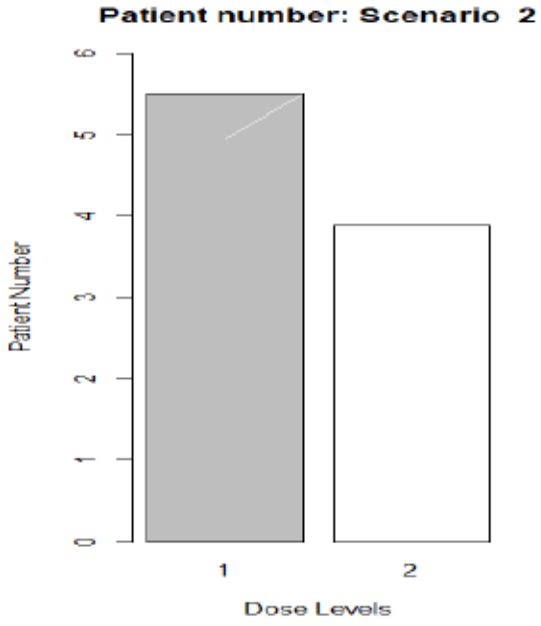




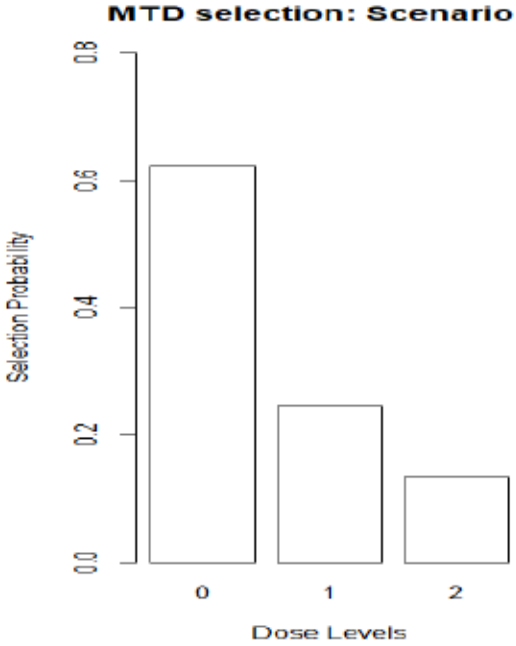
Scenario 1: MTD is 1.25 mg/kg	Possible MTD Dose Level			
	No dose is safe	1.0 mg/kg	1.25 mg/kg	
True DLT rate		0.12	0.22	
Mean number of patients at dose level		4.20	5.27	
Mean number of DLTs at dose level		0.52	1.19	P (Select the True MTD) = 0.53 Average DLT rate = 0.19 Average number of patients above MTD = NA
Pr (Chosen MTD)	0.10	0.37	0.53	

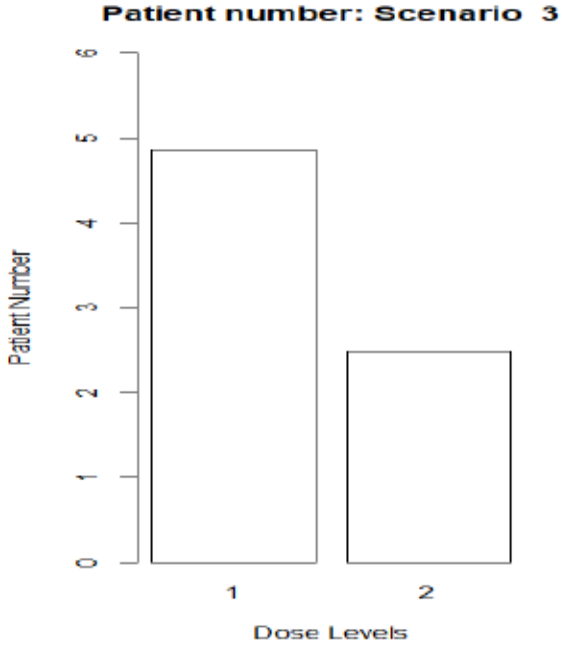
Pr=probability





Scenario 1: MTD is 1.0 mg/kg	Possible MTD Dose Level			
	No dose is safe	1.0 mg/kg	1.25 mg/kg	
True DLT rate		0.22	0.40	
Mean number of patients at dose level		5.50	3.89	
Mean number of DLTs at dose level		1.23	1.57	P (Select the True MTD) = 0.49 Average DLT rate = 0.34 Average number of patients above MTD = 3.9
Pr (Chosen MTD)	0.35	0.49	0.16	





Scenario 1: MTD is 1.0 mg/kg	Possible MTD Dose Level			
	No dose is safe	1.0 mg/kg	1.25 mg/kg	
True DLT rate		0.35	0.4	
Mean number of patients at dose level		4.87	2.48	
Mean number of DLTs at dose level		1.75	0.96	P (Select the True MTD) = NA Average DLT rate = 0.47 Average number of patients above MTD = NA
Pr (Chosen MTD)	0.62	0.25	0.13	

APPENDIX N: NATIONAL KIDNEY FOUNDATION, ESTIMATED GFR CALCULATION

The following calculation is used to determine GFR.

GFR (mL/min/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

- Scr is serum creatinine
- κ is 0.7 for females and 0.9 for males
- α is –0.329 for females and –0.411 for males
- min indicates the minimum of Scr/κor 1
- max indicates the maximum of Scr/κ or 1

From: Levey A, Stevens L, Schmid C, Zhang Y, Castro A, Feldman H, Kusek J, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (2009). A new equation to estimate GFR. Ann Intern Med 150(9): 604-612.

APPENDIX O: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled Single Arm, Open Label Phase 1b/2 Study of SGN-LIV1A in Combination with Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX P: DOCUMENT HISTORY

Version	Date
Original	14-Sep-2017
Amendment 1	29-May-2018
Amendment 2	14-Aug-2018
Amendment 3	07-Feb-2019
Amendment 4	14-Jun-2019
Amendment 5	28-Feb-2020
Amendment 6	24-Jul-2020
Amendment 7	12-Oct-2020
Amendment 8	05-Mar-2021
Amendment 9	09-Nov-2021
Amendment 10	24-May-2022

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page	Change of medical monitor contact info	Update to study personnel
Protocol Synopsis, Figure 1, 3.2, 4.1, 7.4.1, Appendix A	Specified that patients with inaccessible tumors may submit archival tumor samples during screening if collected after completion of prior therapies.	Clarification
Protocol Synopsis, Figure 1, 3, 7.2, Appendix A	Imaging visit schedule changed from a clinic-visit-based schedule to a calendar-based schedule	Keeps imaging schedule more consistent in the event of patient dose delays.
Protocol Synopsis, Appendix A	Specified that patients who discontinue treatment will be followed until progression or start of a new cancer therapy	Clarification
Protocol Synopsis, 3.1.1, 3.1.2, 9.3.10	Addition of an ISMC to review cumulative safety data	Additional measure to ensure patient safety
Protocol Synopsis, 4.1	Changed requirement for 12 months to have elapsed between prior treatment with curative intent and disease recurrence. This period is now 6 months.	New data indicate that a 6 month period is more aligned with other recent and ongoing clinical trials in this population.
Protocol Synopsis, 7.4, Appendix C	Replacement of "Adaptive TCR" with "clonality of TCRβ" to the biomarker assessments list and addition of TCRβ immunoSEQ analysis to methods of analysis list	Clarification
Protocol Synopsis, 3.1.1	Reworded explanation of total patient numbers and expected numbers to be enrolled at the recommended dose	Clarification
List of Abbreviations and Definitions of Terms	Addition of ISMC	Updated to include a new term used in the document
1.6	Sentence was added regarding the sponsor's acknowledgement that no preclinical data have been generated to characterize antitumor activity with LV and pembrolizumab combination therapy.	Clarification
Figure 1, 6.3, 7.4.1, Appendix A, Appendix C	Timing of on-treatment biopsy changed from C1D5 for all patients to C1D5 for patients in Part A and C1D15 for patients in Part B.	Recent data from other studies support analysis of biomarkers over a wider range of time.
3.1.3, 5.2.5	Changed "treatment with LV or pembrolizumab" to "treatment with LV and pembrolizumab"	Correction
3.1.3	Added the phrase "exceptions noted below" to the first criteria for DLT	Clarification
3.2	Added "in addition to RECIST" to explanation of iRECIST response criteria	Clarification
4.1	Specified units for eGFR as mL/min/1.73 m^2	Correction
5.2.3	Added a window of allowable time for LV infusion to occur	Provides further guidance to sites and supports consistent infusion times across the study

Section(s)	Change	Rationale
5.2.5	Changed "delays of >14 days must be discussed with medical monitor" to "delays of >14 days must be approved by medical monitor"	Supports consistency in dosing across the study
Table 1	LV dose modification changes to elevated blood glucose and neutropenia	Enhancement of patient safety based on updated understanding of drug effects; clarification regarding neutropenia
Table 2	Pembrolizumab dose modification changes to myocarditis, nephritis, other immune-related Aes	Enhancement of patient safety based on updated understanding of drug effects
5.5.2, 5.5.3	Added criteria to permit concomitant radiotherapy	Feedback from investigators to better align with standards of care
5.7	New section added on management of hyperglycemia	Enhancement of patient safety based on updated understanding of drug effects
6, 7.5.3, Appendix A	Specified which laboratory tests are to be performed centrally and/or locally	Clarification
6.2, Appendix A	Specified criteria for repeat testing of HbA1c or referral for glucose management	Enhancement of patient safety based on updated understanding of drug effects
6.3	Specified which assessments must be performed predose	Clarification
6.6, 7.5.5, Appendix A	Pregnancy test added at 24 weeks after EOT	Compliance with health authority regulations
6.7	Study closure criteria added	Clarification
7.4.1, 7.4.3	Specified that only US patients will be asked to consent to submission of leftover tissue from unscheduled biopsies and for specimen inclusion in the biospecimen repository. Also specified that patients may withdraw permission for retention of samples at any time	Clarification
7.5.2, Appendix A	Added a measurement of vital signs within 2 hours after each infusion	Enhancement of patient safety
7.5.3	List of clinical laboratory tests updated to include GGT and blood glucose	Clarification
Appendix E	Hormonal birth control methods removed from list of "Acceptable methods" and added to "unacceptable methods" list	Hormonal contraception is contra-indicated in BC patients

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Protocol Synopsis, 3.1.1, 3.2.2, 5.2.3, 5.2.5, 9.1	Changed the maximum dose per cycle for patients dosed at 2.5 mg/kg from 200 mg to 250 mg. In addition, the maximum weight cap was changed from 80 kg to 100 kg	The maximum dose allowable was changed to increase efficacy in patients who weigh >80 kg
Protocol Synopsis, 3.1.1, 3.2.2, 5.2.3, 5.5.1, Table 1, Appendix A	Added language to indicate that prophylactic G-CSF is now mandatory for patients who weigh >80 kg and will be given to patients on the day after study treatment is given, with a visit window of Day 2-4	The increase in the dose cap to 250 mg LV, but requiring growth factors support for patients who will receive >200 mg LV per cycle, should provide a favorable balance of activity and safety for patients receiving LV
List of Abbreviations and Definitions of Terms	Added "mTNBC"	Updated to include a new term used in the document
Figure 1, 4.1, 7.4.1, Appendix A	Removed the biopsy requirement of an 18 gauge needle and added language related to biopsy methods "Core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate."	Clarification
3.1.1	Updated study design to include dose re-escalation language: "Dose re-escalation back to LV 2.5 mg/kg (maximum dose of 250 mg) if 2.0 mg/kg is proven to be safe."	To allow for re-challenge of LV 2.5 mg/kg dosing
3.1.3	Updated DLT criteria to specify that Grade 3 diarrhea and vomiting are not considered DLTs if they resolve to Grade 1 within 3 days. Updated definition of DLT. Added the language "with or without medical assessment" to the following events not to be considered at DLT: fatigue, tumor pain, rash, nausea, and vomiting.	Clarification and alignment with other pembrolizumab combination studies
4.1, 10.1	Added that patient or patient's LAR can provide written informed consent in accordance with local legal requirements	Alignment with the ICFs
4.2	Changed CNS metastases exclusion criteria to only exclude patients with carcinomatous meningitis or active CNS metastases, with the exception of patients whose CNS metastases are adequately treated and who have neurologically returned to baseline for at least 4 weeks prior to enrollment	To reduce exclusion to enrollment
4.2	Added Exclusion Criteria 11 and 22 related to prior radiotherapy and allogenic tissue/solid organ transplant, respectively	Alignment with other pembrolizumab combination studies
5.5.2, Appendix F	Changed "CYP3A4" to "CYP3A" in the list of P-gp and CYP3A inducers and inhibitors	Alignment with other studies within the program
6.3.1, Appendix A	Clarified procedures performed on Day 1	Clarification
6.3.1, 6.3.3, 6.3.4, 6.3.5	Added the assessments "Collection of concomitant medication information" and "Collection of Aes" to Days 5, 8, and 15	To align with the SOE

Section(s)	Change	Rationale
3.1, 6.3.3, Appendix B, Appendix C	Removed Day 5 visit from Part B	To timely align biopsy and PK/PD collection for correlation analysis
6.4, 6.5, Appendix A	Added new section for Response Assessments and new footnote to the SOE stating that response assessments are "Not required if conducted within 4 weeks prior to EOT"	To de-couple response assessments from standard visit days as these assessments no longer relate to visit cycles
7.4.2, 7.5.3	Added tumor markers CEA, CA15-3, and CA27-29 (if already being performed per the site's standard of care) to biomarker assessments	To detect possible pseudoprogression
9.3.6.2, 9.3.6.3	Updated secondary and additional analyses in the document body	To align with the protocol synopsis
Appendix A	Added criteria for a repeat assessment to be obtained if fasting blood glucose is elevated during screening and added footnotes for timing of response assessments and reference to the lab manual for information on sample collection	Clarification
Appendix C	Added footnote "If additional tests, including but not limited to tumor marker assessments, are performed as part of standard of care, please submit those results."	Clarification
Appendix F	Updated list of P-gp and CYP3A inhibitors	To comply with the updated 2016 FDA table for P-gp and strong CYP3A inhibitors
Appendix G	Updated New York Heart Association classification language to align with online source	Clarification
Appendix K	Changed calculation used to determine GFR	Clarification

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Protocol Synopsis Figure 1 foot note, 3.1, 6.4, 7.2, Appendix A	Changed radiographic exam to be every 6 weeks for 12 months	The radiographic exam period was shortened between 6-12 months to more accurately measure PFS
Protocol Synopsis, Figure 1 foot note, 3.1, 6.4, 7.2, Appendix A	Increased radiographic exam window after 12 months from ± 3 days to ± 7 days	To provide more flexibility to patients
Protocol Synopsis Figure 1 foot note	Confirmed objective responses to be at least 4 weeks after documented response	Simplify requirement
Protocol Synopsis, 3.1, 5.3.5.3	Updated pembrolizumab maximum dose to include 35 cycles or 24 months, whichever occurs first	Updated to reflect current prescribing recommendations of pembrolizumab
3.1	Study schedule will be the same for Parts A and B except for Cycle 1 Day 3 and Day 5	Updated to reflect new PK requirements
3.1	Removed sentence about LIV-1 positive patient definitions	Patients are not screened for LIV-1
3.1.3	Added Grade 4 to Aes not considered a DLT for rash, nausea, diarrhea, and vomiting	To enhance patient safety
4.1	For patients who do not have tissue sample available, discuss with medical monitor.	To reduce exclusion to enrollment
4.2	Edited language regarding exclusion for radiation therapy within 2 weeks	Clarification
5.2.5	Allow dose delays for a clinically-significant, unresolved AE on Day 1 of any cycle, rather than only Cycle 2 and beyond.	Clarification
5.7, 6.2, Appendix A	Patients with hyperglycemia should begin glucose management before starting study or within one week of starting treatment. Patients are not required to have a referral.	SGN-LVA1A may cause or worsen hyperglycemia, therefore treatment for hyperglycemia should begin prior to or within one week of starting study treatment
6.2, Appendix A	Coagulation panel performed during screening instead of baseline visit	Moved to screening to allow site to assess patient eligibility
6.2, 7.1, Appendix A	Removed bone scan requirement	To avoid subjecting patients to possibly extraneous testing
6.3	Removed "of each cycle" after Cycle 1 heading	Clarification
6.3.1, Appendix A	Added procedures can be performed up to 2 days prior Day 1 in Cycle 2 and beyond; Added windows to footnotes for Day 1 activities in Appendix A to match text in 6.3.1	Alignment to previous protocol (Amendment 1); Clarification
6.3.1, Appendix A	HbA1c not required on Day 1	Requirement met at screening
6.3.1, 6.5, Appendix A	Coagulation panel not required on Day 1 or EOT	Requirement met at screening
6.3.1, Appendix C	Changed predose blood samples for biomarkers required for Cycles 1, 2, and 3 only	Limit samples to what can reasonably be analyzed.
6.3.1, Appendix B	Changed predose blood samples for PK and ATA required for Cycles 1, 2, 3, 4, 5, and every 5 cycles thereafter	Added to better assess PK and ATA (immunogenicity)

Section(s)	Change	Rationale
6.3.1, Appendix B	Changed postdose blood samples for PK required for Cycles 1, 2, and 4	Collections in Cycles 6 and 8 are no longer required.
6.3.2, Appendix B	Day 3 added for Part B Cycle 1. Required for US patients, optional for ex-US patients. Blood samples for PK	Added to capture MMAE maximum concentration
6.3.3, 6.3.4, 6.3.5	Removed blood samples for biomarkers on Days 5, 8, and 15	Limit samples to what can reasonably be analyzed.
6.3.4, 6.3.5, Appendix A	Safety labs (CBC and serum chemistry) only required in Cycles 1-4	To avoid subjecting patients to possibly extraneous testing
6.5, Appendix A	Remove EOT ECG requirement	To avoid subjecting patients to possibly extraneous testing
7.5.1.1	All Aes must be reported after consent form is signed	Changed to match AE reporting language throughout document
7.5.1.2	Changed AE reporting	To ensure that reported Aes do not arise exclusively from disease progression
9.3.1.7	DE analysis defined	Clarification

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Protocol Synopsis, Figure 1: SGNLVA-002 study schema, 7.4.1	Additional language added to tissue biopsy requirement.	Clarification
Protocol Synopsis, 3.1.2, 3.2, 3.2.1, 7.5.3, 9.1, 9.3.10	Addition of Part B Cohort 2 with continuous monitoring for risk-benefit profile. Refer to Part B Cohort 1 as "MAD" instead of "recommended dose."	To assess the optimal dose of LV in combination with pembrolizumab
Protocol Synopsis, 3.1.1, 3.2, 3.2.2.1, 5.2.3, Table 5: Required dose modifications for LV-associated toxicities, 5.5.1, 9.1	Removed references to maximum LV dose in mg and replaced with weight cap (except in Section 5.2.3 and if referencing G-CSF treatment).	Clarification
Protocol Synopsis	Added "until death or study closure, whichever occurs first" to length that patients will be followed.	Clarification
Protocol Synopsis, 3.1.1, 3.2, 3.2.2.1, 5.2.3, 5.2.5, Table 5: Required dose modifications for LV-associated toxicities, 9.1	Added "and later" after sections qualifying changes with Amendment 2	Update language to reflect additional amendments.
Protocol Synopsis, 9.3.6.1, 9.3.6.3	Changed primary analyses of LIV-1 positive patients to exploratory analysis	Primary analysis is based on all-comers
List of Abbreviations and Definitions of Terms	Updated abbreviations table	Updated table to match current protocol
1.5, 1.5.1, 3.2.2.2, 3.2.2.3	Updated pembrolizumab background	Updates made per Merck requirements
1.6	Addition of Anti-PD(L)1 language in rationale for study	Updated to fit current treatment landscape
3.2.2.1	Clarified language around neutropenia SAE	Clarification
4.1	Removed language from inclusion criteria 4: "measurable disease ~~per computed tomography (CT) scan~~ as defined by RECIST v1.1…"	Clarification per RECIST v1.1
5.2.5	Added third dose reduction of 1.25 mg/kg	Allow 2 dose reductions for patients that start at 2.0 mg/kg
Table 5: Required dose modifications for LV-associated toxicities, 5.7, 6.2, Appendix A	Added management of hyperglycemia language	Clarification
6.2, 6.2.2, 6.2.3.1, 6.2.3.4, 6.2.3.5, 6.5, 7.5.3, Appendix A	Add use of central laboratory for Part B Cohort 2	To allow results to be analyzed by the central laboratory

Section(s)	Change	Rationale
Protocol Synopsis, Figure 1: SGNLVA-002 study schema, 7.4.1	Additional language added to tissue biopsy requirement.	Clarification
6.2.3.4, 6.2.3.5, Appendix A	Remove all D15 safety draws (PK and biopsy remain) and change D8 draws to Cycle 1-2 only	Reduce blood draw burden for patients
7.2, Appendix A	Addition of BICR for Part B Cohort 2	Allow for option of independent review of scans
7.4.1	Added 25 slide FFPE requirement	Provide adequate tissue for biomarker data
7.4.1, 7.4.2	Removed "central" before "laboratory manual"	Clarification
7.5.1.1	Clarify that only study protocol-related AEs are reported after informed consent before treatment initiation	Clarification
7.5.1.2	Changed language regarding investigating potential causes of hepatotoxicity to "consider holding study drug"	Update to standardized language
7.5.3	Removed LDS and GGT from list of chemistry panel (tests previously removed from protocol)	Correction
Appendix B	Changed Appendix B cycle column to reflect schedule in text	Correction

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Synopsis, 2, 3.1, 3.1.3, 3.1.4.2, 3.2, 3.2.1, 3.2.3.2, 3.2.3.3, 5.2.3, 5.2.5, 5.2.3.2, 5.2.5.2, 5.5.1, 5.5.2.1, 5.5.3, 5.7, 6.3, 6.5, 7.4.1, 7.5.2, 7.5.3, 9.1, 9.1.3, Appendix C, Appendix D, Appendix E, Appendix M	Added a weekly LV dosing schedule (Part C). Affected sections include - Objectives and endpoints - Study design - Dose-limiting toxicity - Rationale for study design - Method of assigning patients to treatment groups - Rationale for selection of doses - LV dose and administration - LV dose modifications - Required concomitant therapy - Prohibited concomitant therapy - Management of hyperglycemia - Study activities - Biomarkers in solid tumor tissue - Determination of sample size - PK, ATA, and biomarker sampling time points for Part C - mTPI interval design simulation report	To evaluate weekly LV dosing in combination with pembrolizumab
Synopsis, 3.1, 6.6, Appendix A	Changed frequency of follow-up visits from every 12 weeks to every 6 weeks for the first year on study until disease progression or initiation of a new therapy. After 1 year on study, the frequency of follow-up visits will be reduced to every 12 weeks.	To improve efficacy monitoring
3.1	Intrapatient dose escalation or de-escalation to a dose level shown to be safe may be permitted with sponsor approval in the event that a patient tolerates study treatment.	To allow optimal dosing for patients who tolerate study treatment
3.1.1, 3.2.3.1, Appendix A	Clarified that the maximum weight cap and dose cap are per infusion, not per cycle.	Clarification
5.2.3.3, 6.2.3, 6.3.3, Appendix A	Added LV dosing criteria	To specify minimum criteria to be met prior to LV dosing
5.2.5	Updated dose modifications: Patients who experience DLT in Cycle 1 (the DLT evaluation period) should not receive further treatment with LV and pembrolizumab unless clinical benefit is ~~demonstrated with~~ observed and the AE(s) is adequately managed ~~toxicity~~ with severity improving to Grade 1 or lower. Subsequent doses will be defined by the medical monitor in discussion with the site investigator in the context of the type of AE(s) observed. In the event a patient is unable to tolerate their dose level, additional treatment cycles (Cycle 2 or later) may be administered at a lower dose	Clarification and to align with current LV dose modification recommendations

Section(s)	Change	Rationale
	level. Consultation with the medical monitor is strongly encouraged.	
6.2.1, 7.1	Removed serology for hepatitis C and specified that PCR for hepatitis C viral load should be performed at screening	To align with exclusion criteria
6.2.1, 6.3.1, 7.1, 7.5.3, Appendix A, Appendix C	Added activated partial thromboplastin time (aPTT) to screening assessments	To align with inclusion criteria
Appendix G	Updated guidance on contraception	To align with European guidance
Throughout protocol	Minor corrections and clarifications	Correction and clarification

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Synopsis, Table 1, 3.1.3, 5.2.3.2, Table 5, Appendix C	Revised language to state that the maximum dose of LV in Part C is 200 mg per infusion.	To align with current guidelines for LV.
Synopsis, 3.1.2, 3.2.3, 5.2.3.1, 5.5.1, 5.5.2, 5.5.2.1, Appendix C, Appendix L	Added language clarifying that prophylactic G-CSF therapy is only required for Parts A and B.	Correction and clarification and to align with current guidelines for LV.
Synopsis, 3.1, 5.3.5.3	Updated pembrolizumab maximum dose to include 35 cycles (approximately 2 years).	Updated to reflect current prescribing recommendations of pembrolizumab.
Synopsis, 6.6	Added text to state the follow-up visits will also be discontinued for patients who initiate a new anticancer treatment for consistency with the rest of the protocol.	Correction and clarification.
Synopsis, 3.2.3	Added language clarifying that the weight cap applies to Parts A and B only.	Correction and clarification.
5.2.3.3	Added language to correct to LV dosing criteria and to refer to dose modifications tables: Total bilirubin ≤ Grade 12 Additional information on LV dose modifications can be found in Table 3 and Table 5. Please see Table 6 for information on pembrolizumab dosing.	Correction and clarification.
5.2.5.2	Corrected the dose withholding example.	Correction.
Table 5	Revised language to correct inconsistencies and clarify dose modifications.	Correction and clarification.
Table 6	Revised language for pembrolizumab dose modifications.	Updated to reflect current prescribing recommendations of pembrolizumab.
5.5.1, 5.5.2	Removed text from Section 5.5.1 that was duplicated in Section 5.5.2. Moved text "Additional vaccination during the course of the study treatment must be discussed prior to administration with the medical monitor" to Section 5.5.2.	Correction and clarification.
6.3.3, 7.3	Corrected appendix links for PK and ATA samples.	Correction.
6.3.3.3, 6.3.3.4, Appendix C	Added serum chemistry panel collection to Day 8 and Day 15 during Cycles 1 and 2 in the weekly dosing schedule.	To align with current guidelines for LV.
7.2	Added text stating that images from Part C will be collected by a BICR.	Correction.
7.5.1.2	Removed "or are the result of a protocol-specified intervention, such as a procedure" from the pregnancy section.	Correction.
7.5.5, Appendix C	Revised text to clarify that pregnancy tests must be performed within 3 days prior to each Day 1 study drug dose at each cycle.	Correction and clarification.

Section(s)	Change	Rationale
Appendix G	Added text clarifying that contraception should be used until at least 6 months after the final dose.	Correction.
Appendix L	Revised appendix text to align with other Seattle Genetics protocols that use LV.	Correction and clarification and to align with current guidelines for LV.
Throughout protocol	Minor changes to correct inconsistencies, correct and add cross-references, fix typographical errors, and clarifications.	Correction and clarification.

Summary of Changes in Amendment 7

Section(s)	Change	Rationale
List of Abbreviations and Definitions of Terms	Addition of SUSARs	Updated to include a new term used in the document
Table 3	Revised the dose modifications table	Corrections and clarifications
Table 5	Revised the q1wk dose modifications table	Corrections and clarifications
5.5.2	Added text: WBC growth factor support, including primary or secondary prophylaxis and treatment, is strongly encouraged per the ASCO 2015 Update (Smith 2015) (see Appendix L), with the exception of primary prophylaxis (Cycle 1 use) in patients enrolled ~~during~~ in the dose escalation ~~in Part C~~ parts (with the exception of patients who receive >200 SGN-LV1A mg per infusion).	Correction.
7.5.1.5	Updated the sponsor safety reporting section to align with current protocol template language on reporting SAEs: Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.5.1.4). The sponsor will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements.	To align with regulatory guidance
Throughout protocol	Minor corrections and clarifications	Correction and clarification

Summary of Changes in Amendment 8

Section(s)	Change	Rationale
Synopsis, 3.1.3, 9.1, 9.1.3	Added 40 patients to Part C	Enlarge database to better define and inform LV + Pembrolizumab safety and efficacy
Table 7	Updated pembrolizumab dose modifications table.	To align with updated guidelines.
Throughout protocol	Minor corrections and clarifications	Correction and clarification

Summary of Changes in Amendment 9

Section(s)	Change	Rationale
Synopsis, 3.2, 3.2.4, 3.3, 3.3.1, 3.3.3.4, , 5.3.3.4, 5.3.3.5, 5.3.5.3, 5.6.2.1, 5.8, 6.4, 6.4.1, 6.4.3.4, 6.6, 7.2, 7.3, 7.4, 7.5.1, 7.6.3, 9.2, 9.2.4, Figure 2, Table 6, Appendix C, Appendix D, Appendix E	Added a new schedule of 1.5 mg/kg LV dosing on Days 1 and 8 every 21 days (Part D). Affected sections include - Study design - Rationale for study design - Method of assigning patients to treatment groups - Rationale for selection of doses - LV dose and administration - LV dosing criteria - LV dose modifications - Allowed concomitant therapy - Management of hyperglycemia - Study activities - Study assessments - Blinded independent central review (BICR) of imaging - Biomarker sampling in solid tumor tissue - Clinical laboratory tests - Determination of sample size	To evaluate 1.5 mg/kg LV dosing on Days 1 and 8 (off Day 15) in combination with pembrolizumab.
Synopsis, 4.2, 7.2, Appendix C	Added eligibility criterion for Part D patients with mTNBC in the LA/MBC setting who also have PD-L1 CPS<10 to the inclusion criteria and that PD-L1 status will be determined locally at the investigative site using the PD-L1 IHC 22C3 pharmDx FDA-approved test.	To assess the safety and activity of 1.5 mg/kg LV dosing on Days 1 and 8 (off Day 15) in combination with pembrolizumab in patients with mTNBC in the LA/MBC setting who have PD-L1 CPS<10.
Synopsis, 6.4.1, 7.2, 7.5.1, Appendix C	Clarified that archival or fresh tumor tissue is required across all parts of the study for central assessment of exploratory biomarker analyses as well as for local assessment of PD-L1 for eligibility of Part D patients.	To ensure appropriate tumor tissue is available for assessment of eligibility for Part D patients and for assessment of exploratory biomarker analyses.
Synopsis, 9.2, 9.2.4	Added 40 patients to study in Part D and also, changed overall enrollment from 149-161 patients to 189-211.	To ensure sufficient patients are evaluated to determine the safety and activity of 1.5 mg/kg LV dosing on Days 1 and 8 (off Day 15) in combination with pembrolizumab in patients with mTNBC in the LA/MBC setting who have PD-L1 CPS<10.
Synopsis, 3.2.1, 7.6, 9.4.10	Added that the ISMC included sponsor representatives.	Clarification.
6.4.3.4	Added that only CBC will be done for Part D on Day 15 Cycles 1 and 2.	To evaluate patient hematology panel on Day 15 following receiving LV on Days 1 and 8.
Synopsis, 9.4.1.7, 9.4.6, 9.4.6.1	Removed the ITT analysis set and made the all treated analysis set the primary set for efficacy analysis.	To align with a recent amendment to the Statistical Analysis Plan.

Section(s)	Change	Rationale
Synopsis, 9.4.6, 9.4.6.2, 9.4.6.3	Changed the language 'secondary efficacy analyses' as 'additional analyses of efficacy endpoints' and removed the ITT and all treated patients analysis sets for those analyses to clarify that the EE analysis set would be used for these additional analyses as appropriate.	To align with a recent amendment to the Statistical Analysis Plan.
3.2.5, 3.3.1	Added rationale for no DLT evaluation of the Part D regimen	To provide a scientific explanation as to why a DLT evaluation of the Part D regimen is not needed.
3.3.3.4	Added rationale for the patient population for Part D patients with mTNBC in the LA/MBC setting who also have PD-L1 CPS<10	To provide scientific rationale
5.3.3.1	Created a section for 'All Parts' under Section 5.2.3 Dose and Administration and moved language from under 'Parts A and B' that is applicable to all parts of the study to the new section, including language regarding infusion rates and weight-based dosing.	Correction.
7.4	Addition of measurements of concentrations of total antibody in plasma and also that related analytes of LV may be measured using appropriate assays	To provide additional data on LV in plasma.
7.5.1	Changed that if no block is available, that 25 slides may be submitted only with medical monitor approval.	Because archival tissue block is preferred if fresh biopsy is not an option for eligibility of Part D, therefore, all other alternatives must be approved by the medical monitor.
9.4.2	Changed the language of 'discontinued from' to 'came off' study.	To be inclusive of patients who were lost to follow-up.
Synopsis, 9.4.10	~~For Part B Cohort 2,~~ continuous monitoring of the benefit-risk profile will be conducted and continuation of enrollment to the cohort may be altered depending on the benefit-risk profile	Continuous monitoring of the benefit-risk profile applies to all parts of the study.
Appendix M	Updated the link for the implementation programs for the modified toxicity probability interval method	Correction.
Throughout protocol	Minor corrections and clarifications	Correction and clarification.

Summary of Changes in Amendment 10

Section(s)	Change	Rationale
Title page	Updated medical monitor contact information	Personnel change.
Protocol Synopsis 4.1, 6.3.1, 7.1, Appendix C: Footnote V	Removed the requirement to use the PD-L1 IHC PharmDx FDA-approved assay to determine PD-L1 CPS <10 in Part D. Investigative sites can now determine PD-L1 CPS <10 by a PD-L1 IHC assay using the 22C3 clone.	After implementation of the PD-L1 IHC PharmDx FDA-approved assay requirement, it was found that the majority of US and Rest of World investigative sites did not have access to this assay. Sites were unable to enroll patients on Part D. The sponsor subsequently determined that using a PD-L1 IHC assay with the 22C3 clone was sufficient to determine CPS <10 status for enrollment.
Appendix G	Removed the following text from Appendix G. Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated	Clarification in response to a request for information from the Republic of Korea Ministry of Food and Drug Safety. Hormonal contraception is contraindicated in breast cancer patients. The sponsor agreed to remove hormonal contraception agents from Appendix G for clarity.
Throughout protocol	Minor corrections and clarifications	Correction and clarification.

Summary of Changes in Amendment 11

Section(s)	Change	Rationale
Title Page	Updated medical monitor information.	Personnel change
Throughout Protocol	Minor corrections and clarifications. "Seattle Genetics" changed to "Seagen Inc."	Correction and clarification
Protocol Synopsis	The following text was added: Responses will be assessed by CT scan and/or magnetic resonance imaging (MRI) scan every 6 weeks (±3 days) for the first 12 months after the first dose of LV and pembrolizumab and every 12 weeks (±7 days) thereafter through the end of the safety follow-up period. No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. All patients, including those with progressive disease, will be followed for survival until the end of the safety follow-up period, death, or study closure, whichever occurs first." After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted every 12 weeks (±2 weeks) starting from the last radiographic scan demonstrating disease progression or from initiation of the new anticancer treatment. Survival follow-up will continue until the end of the safety follow-up period, death, or study closure, whichever comes first. Follow-up may be conducted with clinic visits or telephone calls. No further response assessments are required. Defined "will" with "may" in the following sentence: Patient serum and plasma samples will be obtained for LV PK and ATA evaluation at protocol specified time points. Concentrations of antibody-drug conjugate (ADC) LV and monomethyl auristatin E (MMAE) will be measured in plasma and ATA in serum. Starting with Amendment 11, PK and immunogenicity assessments will not be conducted after Cycle 1. Starting with Amendment 11, biomarker assessments will not be conducted after Cycle 1.	To allow flexibility in data collection of exploratory objectives to reduce trial burden.

Section(s)	Change	Rationale
Section 3.1	The following text was added: Figure 1 footnote a and Figure 2 footnote a: Following end of study treatment, no additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. Figure 1 footnote b and Figure 2 footnote b: Patients who discontinue study treatment in the absence of disease progression will continue to be evaluated for response every 6 weeks until completion of the safety follow-up period (30 days post treatment for LV and 90 days post treatment for pembrolizumab). The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.5.1.2 and Section 7.5.1.4 for patients who are still receiving treatment or in the safety follow-up period. See Section 6.7 for details. Patients will be evaluated for response assessments every 6 weeks (±3 days) for the first 12 months, and every 12 weeks (±7 days) thereafter, regardless of dose delays, thereafter through the end of the safety follow-up period. No additional scans or response assessments are required after the safety follow-up period. Additional scans or response assessments may be performed as part of the patient's standard of care at any time.	Clarification and Update
Section 3.1.1	Replaced "will" with "may" in the following text: Blood samples for PK and immunogenicity analysis may be collected to support the study endpoints. The following text was added: As of protocol Amendment 11, no PK, immunogenicity, PD, or biomarker samples will be obtained after Cycle 1.	Revision and Update
Section 4.4	The following text "Seattle Genetics or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF)" was updated to "Seagen or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and/or case report form (CRF)."	Clarification and Update
Section 4.4.1	The following word "subjects" was replaced with "patients" in the following text: Discontinuation of pembrolizumab may be considered for patients who have attained a confirmed CR that has been treated for at least 8 cycles (24 weeks) and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.	Revision

Section(s)	Change	Rationale
Section 4.4.2	The following text was added: Completion of protocol specified safety follow-up (Section 6.6)	Update
Section 5.5.2, Appendix H	The prescribing information was updated: Based upon evaluation of the anti-CD30 MMAE ADC brentuximab vedotin (Adcetris) (ADCETRIS® Prescribing Information, Seagen, June 2023), concomitant use of P-gp inhibitors or strong cytochrome P450 3A4 (CYP3A4) inhibitors has the potential to increase the exposure to MMAE (the cytotoxic component of LV and brentuximab vedotin).	Update
Section 5.8	The following text "and the CRF" was removed from the following sentence: Study drug administration will be performed by study site staff and documented in source documents and the CRF.	Clarification
Section 6.2.3, Section 6.3.3	All of the Cycles were removed except for Cycle 1.	Clarification
Section 6.4	The following text was added: No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time.	Provide more flexibility to study sites for the treatment and management of patients in the study.
Section 6.6	The following text was added: The following assessments will be conducted at follow-up visits until progression or initiation of a new anticancer treatment through the end of the safety follow-up period. Patients discontinuing treatment will be followed for the protocol required safety follow-up period, unless additional safety concerns warrant further follow up: • 30 days post treatment for LV and • 90 days post treatment for pembrolizumab. No additional follow-up is required after the safety follow-up period. After disease progression or initiation of a new anticancer treatment, survival follow up will be conducted, every 12 weeks (±2 weeks) starting from the last radiographic scan demonstrating disease progression or from initiation of the new anticancer treatment until completion of the safety follow-up period, death, or study closure, whichever comes first. Follow-up may be conducted with clinic visits or telephone calls. No further response assessments will be conducted.	Provide more flexibility to study sites for the treatment and management of patients in the study.

Section(s)	Change	Rationale
Section 6.7	The following text was added: For patients still receiving treatment or in the safety follow-up period, the investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.5.1.2 and Section 7.5.1.4 for each patient.	Provide more flexibility to study sites for the treatment and management of patients in the study.
Section 7.2	The following text was added: No additional scans or response assessments are required after the safety follow-up period, however additional scans or response assessments may be performed as part of the patient's standard of care at any time. Deleted "In addition, images from Part B Cohort 2 and Parts C and D will be collected by a blinded independent central review (BICR) facility for possible future analysis." Added "patients should not discontinue treatment" to the following text: When feasible, patients should not discontinue treatment until progression is confirmed.	Update
Section 7.3	The following text was added: Starting with amendment 11, PK and immunogenicity assessments will not be conducted after Cycle 1.	Update
Section 7.4	Replaced "will" with "may" in the following text: Tumor samples and blood for exploratory biomarkers analyses may be collected at protocol-specified time points (see Appendix E). The following text was added: Starting with amendment 11, biomarker assessments will not be conducted after Cycle 1.	Update
Section 7.4.2	Replaced "are collected" with "may be collected" in the following text: To understand dynamic changes of these soluble biomarkers and their relationship to efficacy and safety, blood samples may be collected at various time points during the study.	Clarification
Section 7.4.3	Replaced "will be retained" with "may be retained" in the following text: For patients in the US who provide additional consent, remaining de-identified unused blood and/or tissue may be retained by the sponsor and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs.	Clarification

Section(s)	Change	Rationale
Section 7.5.1.2	Added “the completion of the safety follow-up period” to the following text below: Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies and lactations that occur from the time of treatment allocation until the completion of the safety follow-up period or 30 days following the last dose of study drug(s) if the patient initiates new anticancer therapy, whichever is earlier.	Revision
Section 7.5.5	Removed the following text “and 24 weeks after EOT (±1 week)” from the following text: For women of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline, within 3 days prior to each Day 1 study drug dose at each cycle, and at the EOT visit.	Clarification
Section 7.6	Replaced “will be performed” with “may be performed” in the following text: Immunogenicity is commonly assessed for biologics; therefore, standard tests may be performed to detect the possible presence of specific antibodies to LV.	Clarification
Section 9.3.2	The following text "the primary analysis will be conducted when all treated patients have been followed for at least 6 months or came off study, whichever comes first” was updated to “the primary analysis will be conducted when all treated patients have come off study.”	Update
Appendix A	Concerning footnote B, added “completion of the safety follow-up period” and “unless otherwise stated”. Concerning footnote F, added “Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11”. Concerning footnote L, added “unless otherwise stated”. Concerning footnote T, added "follow-up will occur every 6 weeks (±1 weeks) 30 days post last treatment for patients on LV only and 90 days for those on pembrolizumab.” Deleted footnote U, "for Part B Cohort 2, response assessments will be collected by BICR for possible future analysis”.	Update
Appendix B	Concerning footnote C, added “Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11.”	Update

Section(s)	Change	Rationale
Appendix C	Concerning row PK/ATA, added Cycle 1 only to "See PK/ATA/Biomarker Tables (Appendix D and Appendix E)" as presented in Appendix C. Concerning footnote B, added "completion of the safety follow-up period" and "unless otherwise stated". Deleted footnote F, "pregnancy test to be performed 24 weeks (±1 week) after EOT". Deleted footnote S, "response assessments will be collected by BICR for possible future analysis." Added footnote V, added "follow-up will occur every 6 weeks (±1 weeks) 30 days post last treatment for patients on LV only and 90 days for those on pembrolizumab".	Update
Appendix D	Concerning footnote C, added "Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11."	Update
Appendix E	Concerning Table 11 footnote C and Table 12 footnote B, added "Biomarker assessments will only be collected during Cycle 1 as of protocol amendment 11."	Update
Appendix G	Deleted the following text, "systemic exposure (at least 6 months after the final dose of study drug; see Section 4.1). the safety follow-up period" and added "the safety follow-up period.	Update
Appendix K	Replaced "in the CRF" with "in the source documents".	Revision