Protocol Number:	SGNLVA-005
Version:	Amendment 04; 02-Nov-2022
Protocol Title:	Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors
Investigational Product:	Ladiratuzumab vedotin
Brief Title:	A Study of Ladiratuzumab Vedotin in Advanced Solid Tumors
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PROTOCOL SYNOPSIS

Protocol Number SGNLVA-005 **Version** Amendment 04; 02-Nov-2022 **Phase** 2	**Product Name** Ladiratuzumab vedotin **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors

Study Objectives

Primary

- Evaluate antitumor activity of LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and LV + pembrolizumab (Part C Arms 2 and 3, Cohort 8 only) as measured by investigator-determined confirmed objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) for all tumor types
- For prostate cancer, evaluate antitumor activity of LV as measured by investigator-determined prostate-specific antigen (PSA) response by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria in addition to ORR

Secondary

- Evaluate the safety and tolerability of LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and LV + pembrolizumab (Part C Arms 2 and 3, Cohort 8 only) as measured by type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Evaluate stability and control of disease as measured by investigator-determined disease control rate (DCR) as measured by RECIST v1.1
- Evaluate durability of response as measured by duration of response (DOR) in subjects who respond to LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and LV + pembrolizumab (Part C Arms 2 and 3, Cohort 8 only) as measured by RECIST v1.1 for all tumors, and investigator-determined PSA for prostate cancer
- Assess progression-free survival (PFS) in subjects who respond to LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and LV + pembrolizumab (Part C Arms 2 and 3, Cohort 8 only) as measured by RECIST v1.1 for all tumors, and by investigator-determined PSA for prostate cancer
- Assess survival as measured by overall survival (OS) in subjects who respond to LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and LV + pembrolizumab (Part C Arms 2 and 3, Cohort 8 only)
- Assess pharmacokinetics (PK) and immunogenicity of LV (Parts A-C)

Additional

- Assess biomarkers of biological activity, resistance, and predictive biomarkers of response

Study Population

Adult subjects with the following advanced solid tumors (Parts A, B, and C):

- Cohort 1: small cell lung cancer (SCLC) (Parts A and B)
- Cohort 2: non-small cell lung cancer-squamous (NSCLC-squamous) (Parts A and B)
- Cohort 3: non-small cell lung cancer–nonsquamous (NSCLC-nonsquamous) (Parts A and B)

- Cohort 4: head and neck squamous cell carcinoma (HNSCC) (Parts A and B)
- Cohort 5: esophageal squamous cell carcinoma (esophageal-squamous) (Parts A and B)
- Cohort 6: gastric and gastroesophageal junction (GEJ) adenocarcinoma (Parts A and B)
- Cohort 7: castration-resistant prostate cancer (CRPC) (Part B only)
- Cohort 8: melanoma (Parts B and C)

Number of Planned Subjects

Up to approximately 414 subjects will be enrolled in the entire study, including up to 72 subjects in Part A (LV 2.5 mg/kg on Day 1 of every 21-day cycle [q3wk] dosing), up to 252 subjects in Part B (LV Day 1, Day 8, and Day 15 every 21-day cycle [q1wk] dosing), and approximately 90 subjects in Part C ([Cohort 8 melanoma only] LV 1.5 mg/kg Day 1 and Day 8 but not Day 15 every 21-day cycle [2q3wk], LV 1.5 mg/kg 2q3wk + 200 mg pembrolizumab q3wk, LV 1.25 mg/kg q1wk + 200 mg pembrolizumab q3wk).

Study Design

This global, open-label, multicenter trial is designed to assess the activity, safety, and tolerability of LV monotherapy for the treatment of solid tumors. The study consists of 3 Parts evaluating subjects in 8 tumor cohorts, summarized in the table below.

- **Part A:** LV administered by intravenous (IV) infusion at a dose of 2.5 mg/kg on Day 1 of each 21-day cycle (q3wk).
- **Part B:** LV administered by IV infusion at a dose of 1.0 mg/kg (Cohort 1 through Cohort 6) or 1.25 mg/kg (Cohort 1 through Cohort 8) on Day 1, Day 8, and Day 15 of each 21-day cycle (q1wk).
- **Part C:** LV administered by IV infusion at a dose of 1.5 mg/kg on Day 1 and Day 8 of each 21-day cycle (2q3wk) as monotherapy (Arm 1) or in combination with 200 mg pembrolizumab administered by IV infusion on Day 1 of each 21-day cycle (Arm 2) or LV administered by IV infusion at a dose of 1.25 mg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle (q1wk) in combination with 200 mg pembrolizumab administered by IV infusion on Day 1 of each 21-day cycle (Arm 3).

	Cohort 1: SCLC	**Cohort 2**: NSCLC-squamous	**Cohort 3**: NSCLC-nonsquamous	**Cohort 4**: HNSCC	**Cohort 5:** esophageal-squamous	**Cohort 6:** gastric & GEJ adenocarcinoma	**Cohort 7:** CRPC	**Cohort 8:** melanoma
Part A	X	X	X	X	X	X		
Part B	X	X	X	X	X	X	X	X
Part C								X

Subjects will be enrolled in Part A until the individual tumor cohorts have 12 subjects or activation of Protocol Amendment 1 at each respective investigative site, whichever comes first. Upon activation of Protocol Amendment 1 at each investigative site, all subsequent subjects enrolled at that site will be in Part B. Subjects in Part A may cross over to Part B with sponsor's approval based on emerging safety and efficacy data.

Part B will assess LV q1wk in the tumor cohorts. The planned dose levels in Part B are 1.0 mg/kg (Dose Level 0) and 1.25 mg/kg (Dose Level +1). Initially, approximately 12 subjects across the tumor cohorts will be enrolled and receive LV 1.0 mg/kg q1wk. Based on collective safety data from the initial 12 subjects and from the concurrently ongoing phase 1 study SGNLVA-001 evaluating LV q1wk in breast cancer, subsequent enrollment in Part B will either:

- Continue enrolling up to 12 subjects in each tumor cohort at LV 1.0 mg/kg q1wk for interim analysis for futility, or
- Enroll an additional 12 subjects across the tumor cohorts to receive LV 1.25 mg/kg q1wk (Dose Level +1) for safety analysis. If tolerability is demonstrated, enrollment will continue to 12 subjects in each tumor cohort at LV 1.25 mg/kg q1wk for interim analysis for futility.

Interim analysis for futility will be performed separately for each cohort after approximately 12 efficacy-evaluable subjects of a given cohort have been treated at a specific LV dose and schedule. Cohorts that successfully pass the interim analysis for futility may, at the sponsor's decision, continue to enroll up to an additional 18 subjects, totaling up to 30 subjects for each tumor cohort at a specific dose and schedule.

Part C will assess LV 1.5 mg/kg 2q3wk dosing as monotherapy (Arm 1), LV 1.5 mg/kg 2q3wk in combination with pembrolizumab (Arm 2), or LV 1.25 mg/kg q1wk in combination with pembrolizumab (Arm 3) dosing in subjects with melanoma (Cohort 8) only. Enrollment for Part C will begin following completion of enrollment for Part B Cohort 8 (melanoma). Each arm will enroll 30 subjects. Eligible subjects will be randomized in a 2:1:1 ratio to Arms 1, 2, and 3, respectively. Thus, of the first 60 subjects, 30 subjects will be enrolled in Arm 1, 15 subjects will be enrolled in Arm 2 and 15 subjects will be enrolled in Arm 3. This will ensure that Arm 1 reaches the target enrollment sooner. Arm 1 will be closed to further enrollment once it reaches 30 subjects, and the randomization will continue between Arm 2 and Arm 3 in a 1:1 ratio until their enrollment targets are reached.

Additional tumor types may be included in this study in future protocol amendments. Alternative dosing regimens, biopsy/biomarkers, and LV-based combinations may be tested in future amendments.

Investigational Product, Dose, and Mode of Administration

Part A (q3wk dosing): LV will be administered at a dose of 2.5 mg/kg as a 30-minute IV infusion on Day 1 of each 21-day cycle. For subjects weighing more than 100 kg, dosing will be capped at 250 mg per infusion. Any subject receiving >200 mg LV per infusion (weight >80 kg) is required to receive prophylactic granulocyte colony-stimulating factor (G-CSF).

Part B (q1wk dosing): LV will be administered at a dose of 1.0 or 1.25 mg/kg as a 30-minute IV infusion on Day 1, Day 8, and Day 15 of each 21-day cycle. The maximum dose will be 200 mg per infusion.

Part C (LV monotherapy or LV plus pembrolizumab combination):

- **Arm 1**: LV will be administered at a dose of 1.5 mg/kg as a 30-minute IV infusion 2q3wk on Day 1 and Day 8 of each 21-day cycle. The maximum dose will be 200 mg per infusion.
- **Arm 2**: LV will be administered at a dose of 1.5 mg/kg as a 30-minute IV infusion 2q3wk on Day 1 and Day 8 of each 21-day cycle. The maximum LV dose will be 200 mg per infusion. Pembrolizumab will be administered at a dose of 200 mg, approximately 60–90 minutes after administration of LV, q3wk on Day 1 of each 21-day cycle.
- **Arm 3**: LV will be administered at a dose of 1.25 mg/kg as a 30-minute IV infusion q1wk on Day 1, Day 8, and Day 15 of each 21-day cycle. The maximum LV dose will be 200 mg per infusion. Pembrolizumab will be administered at a dose of 200 mg, approximately 60–90 minutes after administration of LV, q3wk on Day 1 of each 21-day cycle.

Duration of Treatment

Subjects will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, study termination by the sponsor, pregnancy, or death, whichever comes first.

Efficacy Assessments

For non-prostate cancer subjects, tumor assessment according to RECIST v1.1 will be performed every 6 weeks (±3 days) for the first 12 months after the first dose of LV and then every 12 weeks (±7 days) thereafter. Objective responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4 to 6 weeks after the first documentation of response. For subjects receiving pembrolizumab in Part C, investigators will make treatment decisions based on site assessments of scans using iRECIST.

For prostate cancer subjects (Part B, Cohort 7), PSA will be assessed every 3 weeks (±3 days). Soft tissue tumor assessment by computed tomography or magnetic resonance imaging scan (CT/MRI) and bone scans according to PCWG3 criteria will be assessed every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter.

Pharmacokinetic and Immunogenicity Assessments

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

Biomarker Assessments

Tumor samples and blood will be collected at protocol-specified time points. Target expression by immunohistochemistry (IHC) and RNA will be performed retrospectively and there will be no subject preselection. Biomarker assessments from tumor tissue may include protein expression, gene expression, disease subtype classification, tumor microenvironment, and mutational profile. Assessments in blood samples may include cytokine measurements, immunoassays, and circulating nucleic acids. Methods of analysis may include IHC, polymerase chain reaction (PCR), next-generation sequencing, multiplex immunofluorescence, flow cytometry, immunoassays, and proteomic methodologies such as enzyme-linked immunosorbent assay (ELISA) and microvesicle assessment.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, physical examination findings, vital signs, concomitant medications, pregnancy testing, and laboratory tests. An ongoing, real-time review of subject safety and serious adverse events (SAEs) will be conducted by the sponsor's Drug Safety Department. Adverse event (AE) severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.

Statistical Methods

The primary analysis of the study will be performed separately for each cohort in Parts A, B, and C when all treated subjects in the cohort have been followed for at least 6 months or come off study, whichever comes first. The primary efficacy endpoint of confirmed ORR per RECIST v1.1 will be estimated for each cohort based on the full analysis set (FAS), comprising all subjects who received any amount of study treatment. The point estimate of ORR and 90% exact confidence intervals (CIs) using the Clopper-Pearson method will be provided for each cohort.

For the prostate cancer cohort, the confirmed PSA response rate and 90% exact CI will also be presented. The confirmed PSA response is defined as a reduction from baseline PSA level of at least 50%, measured twice ≥3 weeks apart.

Interim futility analyses will be performed separately for each cohort in Part A and Part B after approximately 12 subjects of a given cohort have been treated with a specific LV dose and schedule (LV q3wk at 2.5 mg/kg, LV q1wk at 1.0 mg/kg, or LV q1wk at 1.25 mg/kg) and are efficacy evaluable post-baseline. Enrollment to each cohort may be held after approximately 12 subjects for interim futility analysis of the respective cohorts. The Bayesian predictive probability of success (PPoS) approach will be used to determine the futility criteria. At the time of each interim analysis, the PPoS will be calculated. A PPoS <10% (i.e., ≤1 response among the first 12 subjects, or ≤3 responses among the first 12 prostate cancer subjects) indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort given the interim result. Based on efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor.

Safety measurements will be summarized by descriptive statistics based on the safety analysis set. The safety analysis set will include all subjects who received any amount of study treatment.

For all the parts, the sample size is not based on power calculation for a formal hypothesis testing but is selected to provide a degree of characterization of commonly occurring AEs in the safety profile and/or a reasonable estimation precision of ORR.

For a sample size of 30 subjects per cohort/arm, assuming confirmed ORR and confirmed PSA response rate for CRPC is between 10% and 50%, the 2-sided 90% exact CI are summarized below:

Confirmed ORR*	90% Exact CI (N=30)
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)

*Including confirmed PSA response rate for CRPC cohort

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

1L	first line
2L	second line
2q3wk	Day 1 and Day 8 but not Day 15 every 21-day cycle
ADC	antibody-drug conjugate
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	anti-retroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	antitherapeutic antibody
AUC	area-under-the-curve
BRAF	B-Raf proto-oncogene serine/threonine kinase gene
C1	Cycle 1
C2	Cycle 2
C4	Cycle 4
C5	Cycle 5
CBC	complete blood count
CBR	clinical benefit ratio
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

CYP3A	cytochrome P450 3A
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
esophageal-squamous	esophageal squamous cell carcinoma
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
Hb1Ac	hemoglobin A1c
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HR+	hormone receptor positive
IB	Investigator's Brochure
ICD	immunogenic cell death
ICH	International Council for Harmonisation
iCPD	confirmed disease progression by iRECIST guidelines
IEC	independent ethics committee
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IHC	immunohistochemistry

IND	investigational new drug
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
iRIS	ICON Results Integration Services
IRR	infusion-related reaction
iUPD	unconfirmed progression by iRECIST guidelines
IV	intravenous
LA/mTNBC	locally advanced and/or metastatic triple-negative breast cancer
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LV	ladiratuzumab vedotin
mAb	monoclonal antibody
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK cells	natural killer cells
NLT	new lesions-target
NLNT	new lesions-non-target
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetics
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death 1 receptor

PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PD(L)1	programmed cell death 1 receptor or programmed cell death ligand 1, collectively
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPoS	predictive probability of success
PR	partial response
PSA	prostate-specific antigen
q1wk	Day 1, Day 8, and Day 15 of every 21-day cycle
q3wk	Day 1 of every 21-day cycle
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS	reactive oxygen species
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
Scr	serum creatinine
SD	stable disease
SJS	Stevens-Johnson Syndrome
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TRK	tropomyosin receptor kinase
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
vc	valine-citrulline
WFI	water for injection

β-hCG	beta human chorionic gonadotropin

1. INTRODUCTION

1.1. 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 breast cancer 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 (Seagen Inc., data on file).

LIV-1 expression has been linked with malignant progression to metastasis and is associated with lymph node involvement in breast cancer (Manning 1994). It 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 2011) (Seagen Inc., data on file). 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 subject samples). Of the 631 fresh or archival metastatic breast cancer (mBC) tumor samples evaluated by IHC analysis in a phase 1 study conducted by Seagen Inc., >90% were positive for LIV-1 expression and 75% had moderate to high expression. In subjects with triple-negative breast cancer (TNBC), approximately 70% of samples had moderate to high expression of LIV-1 (Modi 2018).

1.2. Ladiratuzumab vedotin

Ladiratuzumab vedotin (LV) is an antibody-drug conjugate (ADC), also known as SGN-LIV1A, directed against the LIV-1 antigen that is being developed to treat subjects with solid tumor malignancies. The antibody backbone of LV is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) called hLIV22. This antibody is chemically conjugated to a synthetic analog of dolastatin 10 (monomethyl auristatin E [MMAE]), which is a naturally occurring tubulin-disrupting molecule. The protease-cleavable valine-citrulline (vc) maleimidocaproyl linker covalently attaches MMAE to hLIV22. An average of 4 MMAE molecules are present on each antibody molecule.

1.2.1. Mechanism of Action

The mechanism of action of LV is as follows (Sussman 2014):

- After binding to cell-surface LIV-1, LV is internalized and trafficked through the endocytic pathway to the lysosomes,
- Proteolytic degradation of the drug linker in lysosomes releases MMAE,
- MMAE binds to tubulin and disrupts the cellular microtubule network, arrests cells at the G2/M phase of the cell cycle, prevents cell division, and eventually leads to the death of tumor cells.

Preclinical data also point to important additional mechanisms of action for MMAE-linked ADCs like LV, including drug-induced endoplasmic reticulum stress and subsequent engagement of the immune system, proinflammatory cytokine release, and the recruitment of antigen-presenting cells (eg, macrophages and dendritic cells) into the tumor, which is consistent with immunogenic cell death (ICD) (Cao 2018).

1.2.2. Summary of Preclinical Activity

The pharmacologic effects of LV in vitro, such as cell binding and cytotoxicity in LIV-1-positive cell lines, have been characterized in multiple studies (Sussman 2014). The affinity of LV to the LIV-1 protein is 0.58 nM, while the half maximal inhibitory concentration (IC50) of LV on MCF-7 cells is 6.3 ng/mL.

The antitumor activity of LV has been evaluated in xenograft models of breast, prostate, and cervical cancer (Sussman 2014). Treatment with LV at 3 mg/kg every 4 days for 4 doses resulted in significant tumor shrinkage in a patient-derived breast cancer model (BR0555) compared to a non-binding control ADC (hIg vcMMAE). The antitumor activity of LV observed in the BR0555 model was dose-dependent. LV also demonstrated antitumor activity at similar doses against other LIV-1-positive breast cancer (MCF-7), prostate cancer (PC3) and cervical (HeLa) xenograft models, while the unconjugated parental antibody alone showed no effect.

1.2.3. Summary of Nonclinical Toxicology

The toxicity of LV following intravenous (IV) administration has been evaluated in single- and repeat-dose studies in rats and monkeys. The dose-limiting toxicity (DLT) was bone marrow suppression observed in both animal models, with concomitant reductions in hematology endpoints (predominantly anemia and neutropenia). Dose-dependent toxicities included testes (atrophy and degeneration of seminiferous tubules and lack of spermatozoa), liver (mild biliary hyperplasia, mild portal inflammation, minimal hepatocellular single cell necrosis, and arrested mitotic figures), small intestine (minimal to mild crypt epithelium necrosis), mammary gland (minimal to mild glandular hyperplasia), thymus (moderate to severe lymphoid depletion), kidney (minimal arrested mitotic figures), spleen (mild arrested mitotic figures and moderate hemosiderosis in the red pulp), ovary (arrested follicular development), mesenteric lymph node (lymphocyte depletion), skin, and rectum (inflammation with bacterial colonies likely due to bone marrow suppression).

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 (HNSTD) levels. An additional MMAE-related toxicity, not observed to date in LV studies in monkeys, is decreased number/absent secondary and tertiary ovarian follicles following repeated administration of MMAE-based ADCs. This change is considered to be due to the antiproliferative effect of MMAE and is considered reversible due to the evidence of recovery upon treatment cessation and the lack of effects on primordial follicles. 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 Investigator's Brochure (IB).

1.2.4. Summary of Clinical Study SGNLVA-001: A Phase 1 Trial of LV in Subjects With Locally Advanced/Metastatic Breast Cancer

1.2.4.1. Study Design of SGNLVA-001

This is an ongoing phase 1 dose-escalation and expansion study to define the safety and tolerability of LV in subjects with unresectable locally advanced/metastatic breast cancer. The study is being conducted in 6 parts, each studying different subject populations. Part A is monotherapy including the dose escalation and first expansion cohort. Part B is combination therapy with trastuzumab. Parts C and D are monotherapy at the recommended dose. Part E is monotherapy evaluating LV administered on Day 1, Day 8, and Day 15 every 21-day cycle (q1wk). Part F is monotherapy evaluating LV intermittent dosing given on Day 1 and Day 8 but not Day 15 of every 21-day cycle (2q3wk).

Please see the LV IB for complete information on SGNLVA-001.

1.2.4.2. DLTs and Maximum Administered Dose

Part A of Study SGNLVA-001 assessed dose escalation of LV from 0.5–2.8 mg/kg. A total of 22 subjects were treated in the dose escalation phase. No DLTs were observed during dose escalation up to doses of 2.8 mg/kg. The maximum tolerated dose (MTD) was not reached. Based on safety and activity data observed in the dose escalation and initial expansion cohorts, the recommended monotherapy dose was determined to be 2.5 mg/kg on Day 1 of every 21-day cycle (q3wk) intravenously.

Subjects in Parts A, B, C, and D will receive LV on Day 1 q3wk. Subjects in Part E (monotherapy with q1wk dosing) will receive LV 0.75–1.75 mg/kg on Day 1, Day 8, and Day 15 of every 21-day cycle. Subjects in Part F (intermittent dosing) will receive LV 1.5 mg/kg 2q3wk.

1.2.4.3. Safety in SGNLVA-001

Safety Data of LV Monotherapy q3wk

As of 26 July 2021, LV monotherapy has been evaluated in 191 subjects with mBC with the majority of subjects receiving LV 2.0 mg/kg (n=36) and LV 2.5 mg/kg (n=141) q3wk. The most common treatment-emergent adverse events (TEAEs) occurring in ≥20% of subjects with mBC treated with LV monotherapy using the q3wk schedule (n=191) are shown in Table 1. This includes all patients who received LV monotherapy q3wk from 0.5 mg/kg to 2.8 mg/kg dose.

The most common Grade 3 or higher events were neutropenia (25.7%), anemia (9.9%), fatigue (8.9%), nausea (6.8%), abdominal pain, dehydration, and dyspnea (5.2% each). Serious adverse events (SAEs) were reported in 71 subjects (37.2%) with 36 subjects (18.8%) experiencing SAEs that were considered at least possibly related to LV. The most commonly reported SAEs included abdominal pain (3.7%), dehydration, nausea (3.1% each), neutropenia, vomiting (2.6% each), constipation, and febrile neutropenia (2.1% each) (Seagen Inc., data on file).

Table 1: Treatment-emergent adverse events occurring in ≥20% of subjects treated in Study SGNLVA-001 by preferred term – LV monotherapy q3wk

Preferred Term [a], n (%)	Total (N=191)
Fatigue	112 (58.6)
Nausea	88 (46.1)
Constipation	78 (40.8)
Decreased appetite	72 (37.7)
Peripheral sensory neuropathy	69 (36.1)
Alopecia	68 (35.6)
Diarrhoea	59 (30.9)
Neutropenia	57 (29.8)
Abdominal pain	48 (25.1)
Arthralgia	47 (24.6)
Vomiting	41 (21.5)

[a] MedDRA Version 24.0
Note: For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term
LV=ladiratuzumab vedotin; MedDRA=Medical Dictionary for Regulatory Activities; q3wk=Day 1 every 21-day cycle.
Source: Seagen Inc., data on file.

Safety Data of LV Monotherapy q1wk

As of 26 July 2021, 81 subjects have been dosed with LV q1wk in SGNLVA-001 (20 subjects with 1.0 mg/kg, 52 subjects with 1.25 mg/kg, and 9 subjects with 1.5 mg/kg). LV monotherapy q1wk doses of 1.0 mg/kg, 1.25 mg/kg, and 1.5 mg/kg were safely delivered without DLTs.

The adverse event (AE) profile occurring in >20% subjects (Seagen Inc., data on file) in subjects dosed with LV monotherapy using the q1wk schedule is shown in Table 2. The most common Grade 3 or higher events for all subjects that received LV q1wk were neutropenia (21.0%), fatigue (14.8%), hyperglycemia, neutrophil count decrease (11.1% each), hypokalemia, hypophosphatemia (9.9% each), and nausea (8.6%). SAEs were reported in 35 subjects (43.2%). Of those, SAEs in 17 subjects (21.0%) were considered at least possibly related to LV. The most commonly reported SAEs included fatigue, febrile neutropenia, nausea (3.7% each), abdominal pain, dehydration, hyponatremia, and neutrophil count decrease (2.5% each) (Seagen Inc., data on file).

Table 2: Treatment-emergent adverse events occurring in ≥20% subjects treated in Study SGNLVA-001 – LV monotherapy q1wk

Preferred Term [a], n (%)	1 mg/kg (N=20)	1.25 mg/kg (N=52)	1.5 mg/kg (N=9)	Total (N=81)
Fatigue	12 (60.0)	31 (59.6)	7 (77.8)	50 (61.7)
Nausea	10 (50.0)	31 (59.6)	4 (44.4)	45 (55.6)
Peripheral sensory neuropathy	3 (15.0)	28 (53.8)	5 (55.6)	36 (44.4)
Constipation	8 (40.0)	20 (38.5)	6 (66.7)	34 (42.0)
Decreased appetite	6 (30.0)	23 (44.2)	2 (22.2)	31 (38.3)
Diarrhoea	9 (45.0)	16 (30.8)	4 (44.4)	29 (35.8)
Vomiting	10 (50.0)	16 (30.8)	2 (22.2)	28 (34.6)
Myalgia	4 (20.0)	16 (30.8)	4 (44.4)	24 (29.6)
Neutropenia	4 (20.0)	14 (26.9)	6 (66.7)	24 (29.6)
Abdominal pain	5 (25.0)	17 (32.7)	1 (11.1)	23 (28.4)
Alopecia	5 (25.0)	14 (26.9)	3 (33.3)	22 (27.2)
Hypokalaemia	5 (25.0)	14 (26.9)	3 (33.3)	22 (27.2)
Arthralgia	4 (20.0)	16 (30.8)	1 (11.1)	21 (25.9)
Dyspnoea	4 (20.0)	13 (25.0)	4 (44.4)	21 (25.9)
Weight decreased	3 (15.0)	12 (23.1)	4 (44.4)	19 (23.5)
Muscular weakness	1 (5.0)	13 (25.0)	4 (44.4)	18 (22.2)
Dizziness	4 (20.0)	11 (21.2)	2 (22.2)	17 (21.0)
Insomnia	1 (5.0)	14 (26.9)	2 (22.2)	17 (21.0)

[a] MedDRA Version 24.0

Note: For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term. The 20% cutoff is based on percentages in the "Total" column.

LV=ladiratuzumab vedotin; MedDRA=Medical Dictionary for Regulatory Activities; q1wk= Days 1, 8, and 15 every 21-day cycle.

Source: Seagen Inc., data on file

1.2.4.4. Preliminary Efficacy Data for SGNLV-001

LV q3wk Responses in TNBC Subjects

As of 29 September 2017, 35 of the 60 subjects (58%) treated with LV q3wk in the TNBC monotherapy cohorts achieved a PR (15 [25%] subjects) or stable disease (SD) (20 subjects [33%]) (Modi 2018). The overall response rate was 25% (objective response rate [ORR]) and 28% clinical benefit rate (CBR) (see Table 3).

Table 3: Best response by LV q3wk dose level – TNBC subjects

	Dose level (mg/kg)			
	2.0 (N=31)	2.5 (N=26)	2.8 (N=1)	Total (N=60) [a]
Best clinical response, n (%)				
CR	0 (0)	0 (0)	0 (0.0)	0 (0.0)
PR	4 (12.9)	9 (34.6)	1 (100)	15 (25.0)
SD	12 (38.7)	7 (26.9)	0 (0.0)	20 (33.3)
PD	15 (48.4)	10 (38.5)	0 (0.0)	25 (41.7)
ORR, % (95% CI)	13 (4, 30)	35 (17, 56)	100 (3, 100)	25 (15, 38)
DCR, n (%)	16 (51.6)	16 (61.5)	1 (100)	35 (58.3)
CBR, % (95% CI)	13 (4, 30)	39 (20, 59)	100 (3, 100)	28 (18, 41)

CBR=clinical benefit rate (CR + PR + SD ≥24 weeks); CI=confidence interval; CR=complete response; DCR=disease control rate (CR + PR + SD); ORR=objective response rate (CR + PR); PD=progressive disease; PR=partial response; SD=stable disease; TNBC=triple-negative breast cancer

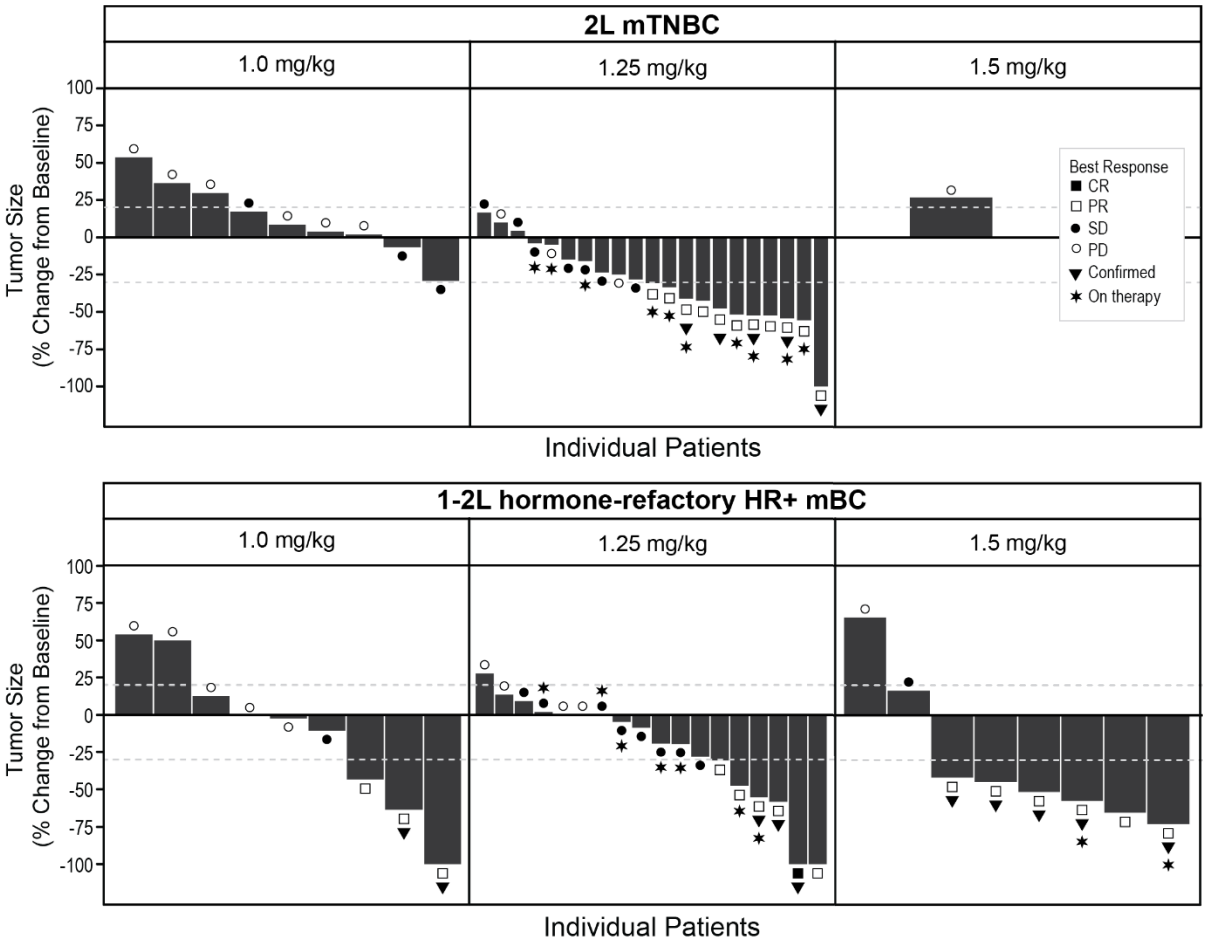
Source: San Antonio Breast Cancer Symposium Poster, December 2017 (Modi 2018).

[a] Response data is shown for efficacy evaluable subjects 2.0 mg/kg and higher doses

LV q1wk Responses in TNBC and HR+ mBC Subjects

Preliminary efficacy results from the LV q1wk dose schedule (Part E) of the SGNLVA-001 study are shown in Figure 1, which demonstrates best percentage change in the sum of tumor diameters from baseline for both subjects with second line (2L) TNBC and subjects with first line (1L) or 2L hormone-refractory hormone receptor positive (HR+) mBC (data cutoff 06-Jan-2021).

Figure 1: Percent change in sum of tumor diameters by breast cancer subtype and dose for Study SGNLVA-001



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

Efficacy results for subjects with 2L metastatic TNBC treated with LV q1wk were available as of 19 March 2021. Twenty-four of the 39 total subjects treated with LV q1wk achieved a PR (8 subjects [21%]) or SD (16 subjects [41%]) (Tsai 2021). Table 4 summarizes the responses according to the dose levels explored in this part of the study.

Table 4: Best response by LV q1wk dose level – 2L TNBC subjects

	Dose level (mg/kg) [a]	
	1.0 (N=10)	1.25 (N=29)
Best clinical response, n (%)		
CR	0 (0)	0 (0)
PR	0 (0)	8 (28)
SD	3 (30)	13 (45)
PD	6 (60)	7 (24)
NE	1 (10)	1 (3)
ORR, % (95% CI)	0 (0, 31)	28 (13, 47)
Duration of response, months (95% CI)	0	2.9 (2.2, 7.0)

[a] LV 1.5 mg/kg q1wk, only 1 LA/mTNBC subject accrued and had PD as best response
CI=confidence interval; CR=complete response; NE=not evaluable; ORR=objective response rate (CR + PR); PD=progressive disease; PR=partial response; q1wk= Day 1, 8, and 15 every 21-day cycle; SD=stable disease; LA/mTNBC= locally advanced and/or metastatic triple-negative breast cancer
Note: unconfirmed PRs are categorized as SD
Source: European Society of Medical Oncology Poster (September 2021)

1.3. Pembrolizumab Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal 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 IB.

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

Justification for the planned dose of pembrolizumab for this study is detailed in Section 3.2.7.

1.3.1. 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). Consequently, the PD-1/PD-L1 (collectively PD[L]1) pathway is an attractive target for therapeutic intervention in solid tumor malignancies like melanoma.

1.3.2. Summary of Pre-Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD(L)1 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).

1.3.3. Summary of Study SGNLVA-002: A Phase 1b/2 Trial of LV Combined with Pembrolizumab in Subjects with LA/mTNBC

1.3.3.1. Study Design of SGNLVA-002

This is an ongoing phase 1b/2, open-label, combination-treatment study and is intended to determine the safety, tolerability, and antitumor activity of LV when used in combination with

pembrolizumab in 1L treatment of subjects with locally advanced and/or metastatic triple-negative breast cancer (LA/mTNBC).

There are 3 treatment schedules in this study: a 2.0 or 2.5 mg/kg q3wk LV plus 200 mg q3wk pembrolizumab schedule, a 1.0–1.25 mg/kg q1wk LV plus 200 mg q3wk pembrolizumab schedule, and a 1.5 mg/kg 2q3wk plus 200 mg q3wk pembrolizumab schedule.

1.3.3.2. Safety in SGNLVA-002

At the time of the data cutoff (26 July 2021), 136 subjects have received LV plus pembrolizumab treatment. Ninety-one subjects have been treated with LV q3wk and 45 subjects with LV q1wk in combination with pembrolizumab.

The most common TEAEs reported in ≥20% of subjects receiving LV q3wk plus pembrolizumab or LV q1wk plus pembrolizumab are shown in Table 5.

Table 5: Treatment-emergent adverse events occurring in ≥20% subjects treated with LV q3wk or q1wk + pembrolizumab in Study SGNLVA-002 by preferred term

Preferred Term, [a] n (%)	LV q3wk+ Pembrolizumab (N=91)	LV q1wk + Pembrolizumab (N=45)	Total (N=136)
Nausea	60 (66)	22 (49)	82 (60)
Fatigue	57 (63)	24 (53)	81 (60)
Diarrhoea	45 (49)	18 (40)	63 (46)
Constipation	41 (45)	15 (33)	56 (41)
Alopecia	45 (49)	10 (22)	55 (40)
Decreased appetite	36 (40)	11 (24)	47 (35)
Peripheral sensory neuropathy	37 (41)	7 (16)	44 (32)
Vomiting	27 (30)	9 (20)	36 (26)
Abdominal pain	26 (29)	9 (20)	35 (26)
Arthralgia	27 (30)	8 (18)	35 (26)
Weight decreased	26 (29)	8 (18)	34 (25)
Hypokalaemia	26 (29)	6 (13)	32 (24)
Cough	25 (27)	4 (9)	29 (21)
Pyrexia	22 (24)	7 (16)	29 (21)
Headache	25 (27)	3 (7)	28 (21)
Alanine aminotransferase increased	18 (20)	9 (20)	27 (20)
Aspartate aminotransferase increased	16 (18)	11 (24)	27 (20)
Pruritus	21 (23)	6 (13)	27 (20)

[a] MedDRA Version 24.0

Please note: Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of investigational product.

The 20% cutoff is based on percentages in the "Total" column.

LV=ladiratuzumab vedotin; MedDRA=Medical Dictionary for Regulatory Activities; q1wk=Days 1, 8, and 15 every 21-day cycle; q3wk=Day 1 every 21-day cycle.

Seventy-one of 91 subjects (78%) treated with LV q3wk plus pembrolizumab and 29 of 45 subjects (64%) treated with LV q1wk plus pembrolizumab experienced National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or higher TEAEs. The most common of these events in all subjects were neutropenia (13%), hypokalemia (12%), fatigue (10%), hyperglycemia, and peripheral sensory neuropathy (9%), (Seagen Inc., data on file).

SAEs were reported in 52 subjects (57%) treated with LV q3wk plus pembrolizumab and of these, 26 subjects (29%) had events assessed by the investigator to be related to either LV or

pembrolizumab. Twenty subjects (44%) treated with LV q1wk plus pembrolizumab reported SAEs and of these, 12 subjects (27%) had events assessed to be related to either LV or pembrolizumab (Seagen Inc., data on file). Out of total subjects in SGNLVA-002, the most common SAEs deemed to be related to either LV or pembrolizumab were abdominal pain (4%), colitis, pyrexia (3% each), acute kidney injury, and diarrhea (2% each).

Please see the LV IB for further details on safety of combination therapy.

1.3.3.3. Preliminary Efficacy Data for SGNLVA-002

As of 07 October 2019, LV q3wk in combination with pembrolizumab achieved a confirmed ORR of 35% (Han 2020). SD was observed in 32 subjects (48%), see Table 6.

Table 6: Preliminary Efficacy for SGNLVA-002: Objective response rate

	Total (N=66)[a]
Confirmed ORR, % (95% CI)	35% (23.5, 47.6)
CR confirmed, n (%)	2 (3%)
PR confirmed, n (%)	21 (32%)
SD, n (%)	32 (48%)
PD, n (%)	8 (12%)
Not evaluable/not done, n (%)	3 (5%)

[a] All subjects whose C1D1 date was at least 3 months before the data extract

CI=confidence interval; CR=complete response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.

Source: San Antonio Breast Cancer Symposium Poster, December 2019 (Han 2020)

1.4. Rationale for Study

LIV-1 expression has been linked with malignant progression to metastasis and is associated with lymph node involvement in breast cancer (Manning 1994). Based on the activity observed in TNBC (Section 1.2.4), LV may also have activity in other solid tumors expressing LIV-1. In order to identify those indications most likely to be successfully treated with LV, we evaluated multiple internal and external sources of data on LIV-1 expression. LIV-1 expression has been detected in a number of cancer types including breast, prostate, melanoma, ovarian, bladder, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), esophageal, and gastric adenocarcinoma. Among the 8 primary indications chosen for this trial, prevalence of LIV-1 expression was as high as 99% (SCLC) and largely above 50%. Prevalence of LIV-1-expressing tumors across cancer subtypes based on RNA is similar to that estimated by protein expression (both IHC and mass spectrometry) (Manning 1988; Manning 1994; Dressman 2001; Tozlu 2006; Unno 2009; Sussman 2011; Zhu 2014; George 2015); (Seagen Inc., data on file).

Patients with advanced solid tumors generally have poor outcomes. Some advances have been made with the introduction of anti-PD(L)1 therapies; however, there remains a high unmet need in patients who progress on anti-PD(L)1 therapies, or patients who are not eligible for

anti-PD(L)1 therapies. Chemotherapy often remains the chosen treatment option for these patients but is associated with poor responses and often high toxicity. LV, with its targeted delivery of a cytotoxic payload, may have enhanced efficacy and safety.

Additionally, there may be benefit in combining LV with pembrolizumab, an anti-PD-1 mAb (Section 3.2.6). Preclinical studies combining other vedotin-conjugated ADC therapies with anti-PD(L)1 agents reported improved efficacy over either drug individually (Cao 2017; Huang 2022). A preliminary report using protein and gene expression data from SGNLV-001 and SGNLV-002 found LV combined with pembrolizumab in subjects with LA/mTNBC had improved infiltration of immune cells to the tumor microenvironment (TME) (Pusztai 2020).

Preliminary clinical findings from the phase 3 Keynote-006 study suggest that rechallenging with pembrolizumab upon disease progression after previous immune checkpoint inhibitor treatment can provide additional disease control in patients with advanced melanoma (Robert 2019). A recent phase 2 study also demonstrated significant antitumor activity and tolerability of pembrolizumab in combination with ipilimumab in patients with unresectable or metastatic melanoma who experienced progressive disease after anti-PD(L)1 immunotherapy (Olson 2021). Furthermore, results from the recent phase 2 LEAP-004 study of lenvatinib plus pembrolizumab demonstrated clinically meaningful and durable responses in patients with advanced melanoma who had progressive disease following previous treatment with anti-PD(L)1 immunotherapy (Arance 2022).

This study is designed to assess the activity of LV in subjects with advanced solid tumors as a monotherapy (Part A, Part B, Part C Arm 1) and in combination with pembrolizumab (Part C Arm 2 and Arm 3).

2. OBJECTIVES

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of LV in subjects with solid tumors. Specific objectives and corresponding endpoints for the study are summarized in Table 7.

Table 7: Objectives and corresponding endpoints

Primary Objective	Corresponding Primary Endpoint
• Evaluate antitumor activity of LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and in combination with pembrolizumab (Part C Arm 2 and Arm 3, Cohort 8 only)	• Investigator-determined confirmed ORR as measured by RECIST v1.1 for all tumor types • For prostate cancer, investigator-determined PSA response by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria in addition to ORR
Secondary Objectives	**Corresponding Secondary Endpoints**
• Evaluate the safety and tolerability of LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and in combination with pembrolizumab (Part C Arm 2 and Arm 3, Cohort 8 only)	• Type, incidence, severity, seriousness, and relatedness of AEs
• Evaluate stability and control of disease	• Investigator-determined DCR as measured by RECIST v1.1
• Evaluate durability of response in subjects who respond to LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and in combination with pembrolizumab (Part C Arm 2 and Arm 3, Cohort 8 only)	• Investigator-determined DOR as measured by RECIST v1.1 for all tumors • For prostate cancer, investigator-determined PSA-DOR
• Evaluate PFS of subjects treated with LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and in combination with pembrolizumab (Part C Arm 2 and Arm 3, Cohort 8 only)	• Investigator-determined PFS as measured by RECIST v1.1 for all tumors • For prostate cancer, investigator-determined PSA-PFS
• Evaluate survival of subjects treated with LV as monotherapy (Part A, Part B, and Part C Arm 1 [Cohort 8 only]) and in combination with pembrolizumab (Part C Arm 2 and Arm 3, Cohort 8 only)	• OS
• Assess PK of LV (Parts A-C)	• Selected PK parameters for LV, total antibody, and MMAE
• Assess immunogenicity of LV (Parts A-C)	• Incidence of ATAs to LV
Additional Objectives	**Corresponding Additional Endpoints**
• Assess biomarkers of biological activity and resistance and predictive biomarkers of response	• Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with LV monotherapy and in combination with pembrolizumab

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This global, open-label, multicenter trial is designed to assess the activity, safety, and tolerability of LV monotherapy for the treatment of solid tumors.

Subjects with the following advanced solid tumors will be enrolled:

Cohort 1: SCLC (Parts A and B)

Cohort 2: NSCLC-squamous (Parts A and B)

Cohort 3: NSCLC-nonsquamous (Parts A and B)

Cohort 4: HNSCC (Parts A and B)

Cohort 5: esophageal squamous cell carcinoma (esophageal-squamous) (Parts A and B)

Cohort 6: gastric and gastroesophageal junction (GEJ) adenocarcinoma (Parts A and B)

Cohort 7: castration-resistant prostate cancer (CRPC) (Part B only)

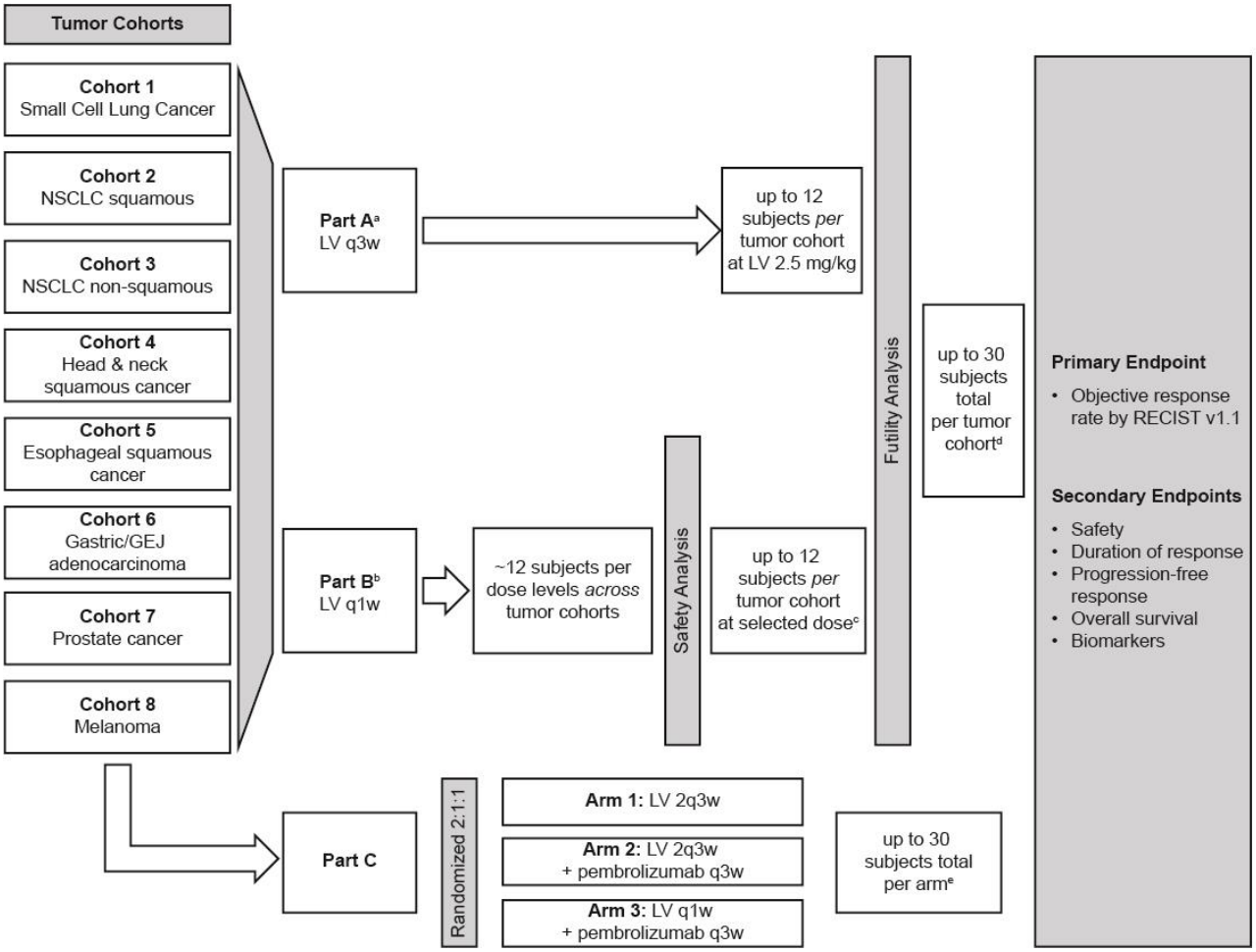
Cohort 8: melanoma (Parts B and C)

The study consists of:

- **Part A** (LV q3wk; Cohorts 1 through 6): LV administered by IV infusion at a dose of 2.5 mg/kg on Day 1 of each 21-day cycle (see Section 5.1).
- **Part B** (LV q1wk; Cohorts 1 through 6 will receive 1.0 mg/kg or Cohorts 1 through 8 will receive 1.25 mg/kg; starting with Protocol Amendment 1): LV administered by IV infusion at a dose of 1.0 mg/kg or 1.25 mg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle (see Section 5.1).
- **Part C** (LV 1.5 mg/kg 2q3wk, LV 1.5 mg/kg 2q3wk plus 200 mg pembrolizumab q3wk, LV 1.25 mg/kg q1wk plus 200 mg pembrolizumab q3wk; Cohort 8 only):
    - **Arm 1**: LV administered by IV infusion at a dose of 1.5 mg/kg on Day 1 and Day 8 but not Day 15 of each 21-day cycle as monotherapy.
    - **Arm 2**: LV administered by IV infusion at a dose of 1.5 mg/kg on Day 1 and Day 8 but not Day 15 of each 21-day cycle in combination with 200 mg pembrolizumab administered by IV infusion on Day 1 of each 21-day cycle.
    - **Arm 3**: LV administered by IV infusion at a dose of 1.25 mg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle in combination with 200 mg pembrolizumab administered by IV infusion on Day 1 of each 21-day cycle.

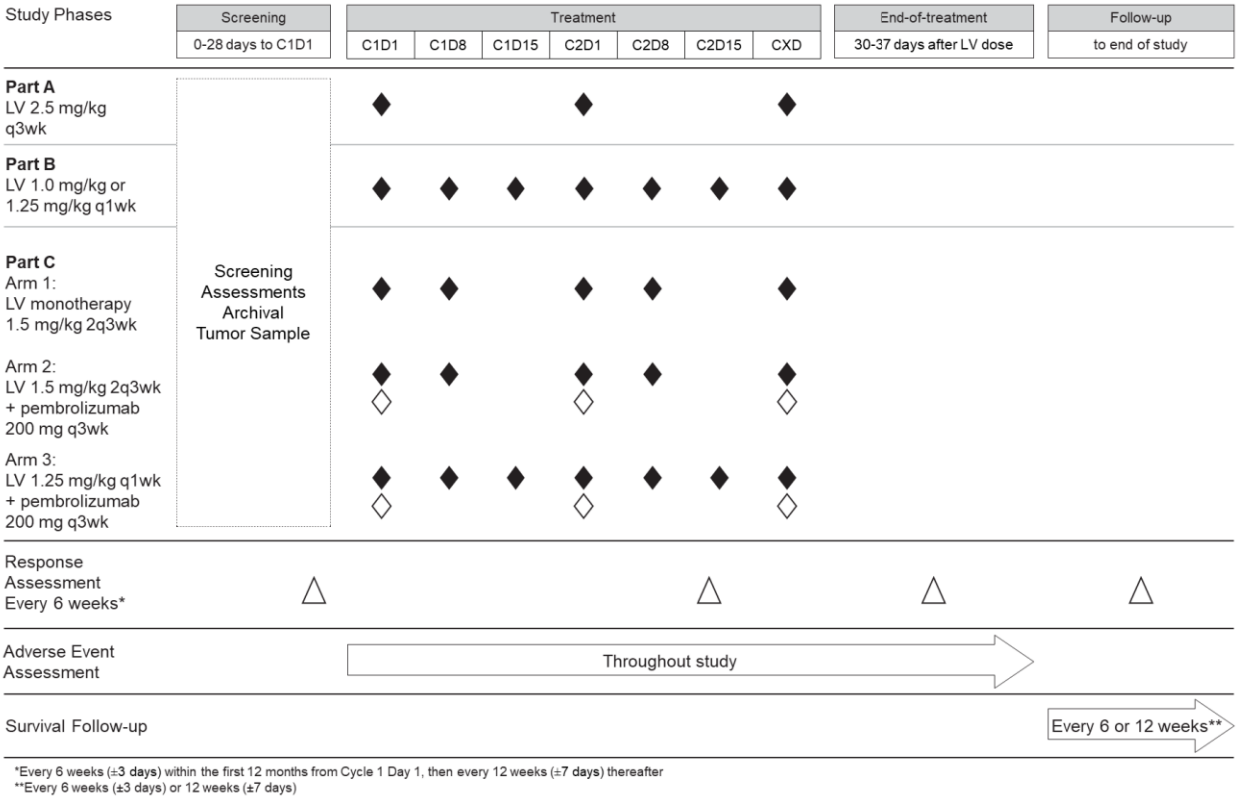
The study design and cohorts for Parts A, B, and C are depicted in Figure 2 and the study schema is depicted in Figure 3.

Figure 2: Study Design and Cohorts – Parts A, B, and C



a Part A will include Cohorts 1 through 6 only.
b In Part B, Cohorts 1 through 6 will receive 1.0 mg/kg LV or Cohorts 1 through 8 will receive 1.25 mg/kg LV (see Section 5.1). The planned LV q1wk doses are 1.0 mg/kg in an initial cohort, to be escalated to 1.25 mg/kg based on safety assessments (details in Section 3.1).
c Includes subjects enrolled prior to and after the safety analysis at a selected LV dose.
d Includes subjects enrolled prior to and after the interim analysis for futility at a selected LV dose and schedule.
e Part C for Cohort 8 will start enrollment upon completion of enrollment for Cohort 8 Part B.
Interim analysis for futility will be performed separately for each cohort of Part A and Part B after approximately 12 efficacy-evaluable subjects of a given cohort have been treated at a specific LV dose and schedule (details in Section 9.3.9).
For Part C, randomization will be stratified according to BRAF mutational status (wild-type vs mutated).

Figure 3: Study Schema Overview



Subjects will be enrolled in Part A until the individual tumor cohorts have 12 subjects or activation of Protocol Amendment 1 at each respective investigative site, whichever comes first. Upon activation of Protocol Amendment 1 at each investigative site, all subsequent subjects enrolled at that site will be in Part B. Subjects in Part A may cross over to Part B with sponsor's approval based on emerging safety and efficacy data.

Part B will assess LV q1wk in the tumor cohorts. The planned dose levels in Part B are shown in Table 8. Initially, approximately 12 subjects across the tumor cohorts will be enrolled and receive LV 1.0 mg/kg q1wk. Based on collective safety data from the initial 12 subjects and from the concurrently ongoing phase 1 study SGNLVA-001 evaluating LV q1wk in breast cancer, subsequent enrollment in Part B will either:

- Continue enrolling up to 12 subjects in each tumor cohort at LV 1.0 mg/kg q1wk for interim analysis for futility, or
- Enroll an additional 12 subjects across the tumor cohorts to receive LV 1.25 mg/kg q1wk (Dose Level +1) for safety analysis. If tolerability is demonstrated, enrollment will continue to 12 subjects in each tumor cohort at LV 1.25 mg/kg q1wk for interim analysis for futility.
- Intrapatient dose escalation to a dose level shown to be safe is permitted with sponsor approval if a subject tolerates study treatment.

Table 8: Planned dose levels for Part B (LV q1wk dosing)

Dose Level	Weekly LV Dose (mg/kg/wk)	Maximum LV Dose in a 21-Day Cycle (mg/kg/cycle)
0	1.0	3.0
+1	1.25	3.75

Interim analysis for futility will be performed separately for each cohort after approximately 12 efficacy-evaluable subjects of a given cohort have been treated at a specific LV dose and schedule (Section 9.3.9). Cohorts that successfully pass the interim analysis for futility may, at the sponsor's decision, continue to enroll up to an additional 18 subjects, totaling up to 30 subjects for each tumor cohort at a specific dose and schedule.

Part C will assess LV as monotherapy and in combination with pembrolizumab in subjects with melanoma (Cohort 8). Enrollment in Part C will begin after Cohort 8 Part B enrollment has been completed. Subjects will be randomized to 1 of 3 arms with 30 subjects per arm. The randomization ratio will be 2:1:1 until Arm 1 reaches 30 subjects. Thus, of the first 60 subjects, 30 subjects will be enrolled in Arm 1, 15 subjects will be enrolled in Arm 2 and 15 subjects will be enrolled in Arm 3. This will ensure that Arm 1 reaches the target enrollment sooner. Afterwards, the remaining subjects will be randomized in a 1:1 ratio to either Arm 2 or Arm 3. Randomization will be stratified according to B-Raf proto-oncogene serine/threonine kinase gene (BRAF) mutational status (wild-type versus mutated).

- Arm 1 (LV monotherapy 2q3wk): subjects will receive 1.5 mg/kg LV on Day 1 and Day 8 but not Day 15 of each 21-day cycle.
- Arm 2 (LV 2q3wk+pembrolizumab q3wk): subjects will receive 1.5 mg/kg LV on Day 1 and Day 8 but not Day 15 of each 21-day cycle and 200 mg pembrolizumab on Day 1 of each 21-day cycle.
- Arm 3 (LV q1wk+pembrolizumab q3wk): subjects will receive 1.25 mg/kg LV on Day 1, Day 8, and Day 15 of each 21-day cycle and 200 mg pembrolizumab on Day 1 of each 21-day cycle.

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 in Solid Tumors Version 1.1 (iRECIST) for subjects in Part C (Arms 2 and 3) (Appendix I).

Additional tumor types may be included in this study in future protocol amendments. Alternative dosing regimens, biopsy/biomarkers, and LV-based combinations may be tested in future amendments.

For non-prostate cancer subjects, tumor assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (Appendix H) will be performed every 6 weeks (±3 days) for the first 12 months after the first dose of LV and then every 12 weeks (±7 days) thereafter. Objective responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4–6 weeks after the first documentation of response.

For prostate cancer subjects (Part B, Cohort 7), prostate-specific antigen (PSA) will be assessed every 3 weeks (±3 days). Soft tissue tumor assessment by computed tomography (CT) or

magnetic resonance imaging (MRI) and bone scans according to the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria will be assessed every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter.

Safety will be assessed throughout the study, and AE severity will be graded using the NCI CTCAE, version 5.

3.1.1. Retreatment

Retreatment of subjects who have progressed on LV monotherapy (Part A, Part B, and Part C Arm 1) or LV plus pembrolizumab (Part C Arm 2 and Arm 3) is not permitted.

3.2. Discussion and Rationale for Study Design

3.2.1. Rationale for Not Selecting Subjects Based Upon Detectable LIV-1 Protein Expression

LIV-1 is expressed in a variety of solid tumors (Section 1.1). LIV-1 expression is detected in the majority of breast cancer subtypes including TNBC (Modi 2018; Yau 2019). An IHC assay for LIV-1 showed that >90% of subjects treated with LV in the phase 1 study of LV monotherapy in mBC had a detectable level of LIV-1. Preliminary analyses comparing the magnitude of LIV-1 expression with response to LV in 2 independent cohorts of the phase 1 study did not show conclusive correlation between LIV-1 expression by IHC and response. To date, 5 out of 15 subjects that tested negative for LIV-1 expression by IHC assay have responded to LV, including 1 of 3 subjects with no detectable LIV-1 (Seagen Inc., data on file).

Biomarker assessments will not be used for subject selection as it is currently not known if expression of LIV-1 or other biomarkers will impact treatment outcome. Based on the experience of LV in mBC as described in Section 1.2.4, LV activity may not be limited to LIV-1 expressing tumors or diminish in the absence of LIV-1 expression. However, in order to understand relationships between the biological characteristics of the tumors chosen for study and subject outcome, pretreatment tumor biopsies will be collected and used for retrospective biomarker assessments.

3.2.2. Rationale for Selection of q3wk LV Dose

LV will be administered at 2.5 mg/kg (maximum dose of 250 mg per infusion) on Day 1 of each 21-day cycle in this open-label study. Dosing is based on the subject's actual body weight, measured at the beginning of each cycle. For subjects weighing >100 kg, dosing will be based on a 100 kg maximum weight (calculated dose not to exceed 250 mg per infusion).

This dose and regimen has been tested in 113 subjects with mBC, including LA/mTNBC, to date, including as 2L treatment in 47 subjects with LA/mTNBC. The regimen has been well tolerated, demonstrating an acceptable safety profile and encouraging clinical activity in the phase 1 study SGNLVA-001 (see Section 1.2.4).

Increasing antitumor activity was observed with increasing dose levels of LV in heavily pretreated LA/mTNBC patients. Confirmed PR, disease control rate (DCR), and median duration of response (DOR) were higher in the 2.5 mg/kg dose level compared to the 2.0 mg/kg dose level.

However, in the 2.5 mg/kg dose cohort, the incidence of neutropenia (Grade ≥3), including febrile neutropenia and serious neutropenia, was higher, particularly at doses >200 mg per infusion. Five of 11 subjects treated at >200 mg experienced SAEs associated with neutropenia. Febrile neutropenia occurred in 2 of 11 subjects, including 1 treatment-related death due to sepsis. No other treatment-related deaths occurred on study. Dose modifications due to AEs were more common at 2.5 mg/kg when receiving >200 mg. In contrast, there were no reported cases of febrile neutropenia or neutropenia associated SAEs in 18 subjects dosed at 2.5 mg/kg when receiving <200 mg.

Therefore, a recommended phase 2 dose of 2.5 mg/kg with a dose cap of 250 mg per infusion was selected, with subjects treated at a >200 mg dose per infusion required to receive prophylactic myeloid growth factor support (eg, granulocyte-colony stimulating factor [G-CSF]) to reduce the rate, severity, and complications of neutropenia, while maintaining the potential for responses.

3.2.3. Rationale for Mandatory G-CSF for Subjects Receiving More than 200 mg LV per Infusion in Part A

As described in Section 3.2.2, evaluation of the 2.5 mg/kg dose indicated that febrile neutropenia was observed more frequently at a dose of 2.5 mg/kg when the total dose was >200 mg than when the total dose was ≤200 mg per infusion (Modi 2018). Thus, subjects who receive a dose of LV >200 mg per infusion will be required to receive prophylactic G-CSF support to reduce the rate, severity, and complications of neutropenia. A recent evaluation demonstrates that primary prophylactic G-CSF has reduced the rate of treatment emergent neutropenia, postbaseline decreased absolute neutrophil count (ANC), and neutropenic infections in subjects receiving 2.5 mg/kg >200 mg LV (Seagen Inc., data on file).

3.2.4. Rationale for Selection of q1wk LV Doses

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

The starting weekly dose of LV in Part B of SGNLVA-005 will be 1.0 mg/kg (Dose Level 0). This LV dose results in a pharmacokinetic area-under-the-curve (AUC) exposure similar to LV of 2.5 mg/kg q3wk. At these similar pharmacokinetic exposures, it is not anticipated that there will be a detriment in the clinical efficacy or safety profile. As described in Section 1.2.4.3, LV has been shown to be tolerable and without any DLTs up to 1.5 mg/kg/week. The safety profile of LV q1wk appears safe and tolerable, with most TEAEs being Grade 1–2 in severity.

Further, while gastrointestinal toxicities (nausea, constipation, diarrhea, and vomiting) were among frequent AEs reported in subjects dosed with LV q3wk (Part A, B, C, and D of the study), LV q1wk appears to result in a numerically lower frequency of gastrointestinal toxicities compared to LV q3wk (Table 1 and Table 2).

In addition, preliminary data indicated that tumor size reductions in breast cancer patients were observed at the lowest dose level evaluated (1.0 mg/kg/week) with increased activity observed at 1.25 mg/kg q1wk (Seagen Inc., data on file).

Pharmacokinetic modeling data derived from over 200 subjects previously treated with LV q3wk suggest improvements in the safety profile of LV q1wk dosing may be due in part to the reduced

maximum concentration (C_{max}) compared to q3wk dosing (Seagen Inc., data on file). In addition, LV q1wk dosing is anticipated to result in higher trough concentration (C_{trough}) 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).

3.2.5. Rationale for Selection of 2q3wk LV Dose (Part C)

LV monotherapy has been extensively evaluated across a range of doses and schedules in subjects with mBC in the concurrently ongoing phase 1 study SGNLVA-001 (see Section 1.2.4.3). In Part E of this study, 81 patients with mBC received LV administered at 1.0, 1.25, or 1.5 mg/kg weekly (q1wk). No DLTs were observed at any of the 3 starting doses evaluated in the dose escalation phase (Seagen Inc., data on file).

Preliminary efficacy results from Part E of the SGNLVA-001 study are shown in Figure 1 in Section 1.2.4.4 (data cut 06-Jan-2021). There appears to be greater magnitude of tumor size reduction with increasing dose of LV q1wk with the 1.5 mg/kg dose having the highest proportion of patients with measurable response. However, the frequency of AEs generally appears to increase with increasing dose as well. Table 2 in Section 1.2.4.3 summarizes the most commonly reported AEs by dose in SGNLVA-001 (26-July-2021, Seagen Inc., data on file). Due to the high frequency of neutropenia at the LV 1.5 mg/kg q1wk dose, (67% of patients with 44% of patients having Grade ≥3), accrual to this expansion cohort was paused. Although higher efficacy had been observed with the 1.5 mg/kg dose level, the better safety and tolerability of the 1.25 mg/kg dose led to further expansion of this cohort.

In the patients treated with LV monotherapy at the 1.25 mg/kg q1wk dose level, the relative dose intensity started to decrease by Cycle 2 (C2) leading to 2 doses being administered in every 3-week cycle. Similarly, most of the clinically significant neutropenia events in the 1.5 mg/kg dose level occurred after 3 weekly doses. Overall, these observations suggested that an LV drug holiday may be needed to mitigate AEs, including neutropenia, for long-term treatment. This is further supported by PK simulation which demonstrated that giving LV 1.5 mg/kg on Days 1 and 8 every 21 days (2q3wk) would result in similar PK exposures as 1.25 mg/kg q1wk dosing schedule. Based on this rationale, the intermittent dosing schedule of LV 1.5 mg/kg 2q3wk is being explored as monotherapy in Part F of study SGNLVA-001.

Additionally, efficacy results from Part C of study SGNLVA-002 evaluating LV at the 1.25 mg/kg q1wk dose level in combination with pembrolizumab q3wk as frontline therapy in patients with LA/mTNBC showed encouraging activity in both PD-L1 high and low/negative disease. Confirmed objective responses were observed in 46% of patients, respectively, with 3 patients (8%) having PD-L1 low/negative disease achieving a CR following treatment with the combination (Seagen Inc., data on file). However, frequent LV dose modifications were observed at the weekly dosing schedule which suggested that treatment holidays may be required for long-term dosing. Part D of study SGNLVA-002 is exploring the intermittent dosing schedule of LV 1.5 mg/kg 2q3wk in combination with pembrolizumab as 1L treatment in patients with PD-L1 low/negative LA/mTNBC (see Section 1.3.3.1).

In the current study SGNLVA-005, LV monotherapy has only been explored at the 1.25 mg/kg q1wk dosing schedule in patients with melanoma (Part B; Cohort 8). Interim results from this cohort showed preliminary signs of activity in this patient population, and the cohort was subsequently opened for expansion according to the prespecified protocol futility analysis criteria. Similar to what was observed in mBC, recent PK modeling based on the first 15 patients enrolled in Cohort 8 treated at the 1.25 mg/kg q1wk dose level also supports further evaluation of the LV 1.5 mg/kg 2q3wk schedule (Seagen Inc., data on file) to improve the overall safety profile and response durability in subjects with advanced melanoma.

3.2.6. Rationale for Combining LV with Pembrolizumab in Part C

Accumulating data suggests chemotherapeutic agents may activate the immune system by inducing tumor cell apoptosis and tumor-associated antigen release, a process termed ICD (Bracci 2014). Tumor-associated antigens are taken up by antigen presenting cells such as dendritic cells or macrophages which then traffic to tumor-draining lymph nodes and activate effector immune cells such as T-cells and natural killer (NK) cells. Activation and infiltration of these immune cells to the TME leads to a potent anti-tumor response.

LV and PD(L)1 inhibitors act through distinct but complementary mechanisms of action. Data from preclinical studies of MMAE ADCs comprising the same linker and MMAE payload as LV, brentuximab vedotin (a CD30-directed ADC) and enfortumab vedotin (a nectin-4 directed ADC), showed potential to induce ICD, antigen presentation, and tumor immune infiltration (Gardai 2015; Liu 2020). These results suggest that the effects are due to the MMAE payload (Gardai 2015; Liu 2020). These ADCs induce hallmarks of ICD with innate immune cell migration and activate adaptive immune response within the TME (Cao 2017; Cao 2018). The addition of immune checkpoint inhibitors, such as a PD(L)1 inhibitor like pembrolizumab, to treatment with MMAE conjugated ADCs can further amplify the adaptive immune response by preventing T-cell exhaustion and loss of inflammatory effector functions, as well as increasing T-cell and NK cell trafficking to the TME (Stagg 2011; Muller 2014; Muller 2015; Huang 2022).

A preliminary report using IHC and gene expression data from SGNLVA-001 and SGNLVA-002 studies that compared LV monotherapy to LV combined with pembrolizumab in subjects with LA/mTNBC showed that when subjects received both LV and pembrolizumab, there was evidence of enhanced immune activation in the TME. This included activation of adaptive immune response pathways and increased infiltration of CD8 T-cells in addition to macrophages (Pusztai 2020).

The antitumor immune response patterns seen with combining immunotherapeutic agents, such as pembrolizumab and LV, 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 assessment of disease progression for immunotherapeutic agents. Therefore, in addition to RECIST v1.1, iRECIST will be used by study sites to evaluate disease progression for determining eligibility of treatment continuation in Part C (Arms 2 and 3) to account for the appearance of possible new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix I).

3.2.7. Rationale for Pembrolizumab Dose

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 an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg q3wk to 10 mg/kg every 2 weeks (q2wk) representing an approximate 5- to 7.5-fold exposure range (refer to the IB)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg q3wk
- Clinical data showing meaningful improvement in benefit-risk including overall survival (OS) 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 NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg 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 Hodgkin Lymphoma, 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.

3.2.8. Blinding and Unblinding

This is an open-label study.

4. STUDY POPULATION

Subjects must meet all 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

Eligibility for each of the solid tumor cohorts are listed below:

- Cohort 1, SCLC (Part A and Part B):
  - Subjects must have pathologically-documented SCLC;
  - Must have extensive stage disease;
  - Must have disease progression during or following prior platinum-based systemic chemotherapy for extensive stage disease;
  - No more than 1 prior line of cytotoxic chemotherapy for extensive disease stage;
  - May have received prior anti-PD(L)1 therapy, unless contraindicated.
  - Mixed SCLC/neuroendocrine tumors with NSCLC histologies are not eligible.
- Cohort 2, NSCLC-squamous (Part A and Part B):
  - Must have pathologically-documented squamous cell NSCLC;
  - Must have unresectable locally advanced or metastatic disease;
  - Must have disease progression during or following systemic therapy;
    - Subjects must have progressed during or after a platinum-based combination therapy administered for the treatment of metastatic disease. Maintenance therapy is permitted provided there was no progression after the initial platinum-based combination. Changing chemotherapy agents during platinum-based treatment for the management of toxicities is permitted provided no progression has occurred while on the initial therapy; or
    - Subjects must have progressed within 6 months of last dose of platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for early stage or locally advanced stage disease.
  - Subjects with known epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species (ROS), BRAF, or other actionable mutations are not eligible;
  - No more than 1 prior line of cytotoxic chemotherapy for their advanced disease;
  - Must have received prior anti-PD(L)1 therapy, unless contraindicated;

- Subjects with mixed histology NSCLC are eligible as long as the tumor is predominantly squamous histology. Mixed SCLC/neuroendocrine tumors with NSCLC histologies are not eligible.

- Cohort 3, NSCLC–nonsquamous (Part A and Part B):
  - Must have pathologically-documented nonsquamous NSCLC;
  - Must have unresectable locally advanced or metastatic disease;
  - Must have disease progression during or following systemic therapy;
    - Subjects must have progressed during or after a platinum-based combination therapy administered for the treatment of metastatic disease. Maintenance therapy is permitted provided there was no progression after the initial platinum-based combination. Changing chemotherapy agents during platinum-based treatment for the management of toxicities is permitted provided no progression has occurred while on the initial therapy; or
    - Subjects must have progressed within 6 months of last dose of platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for early stage or locally advanced stage disease.
  - Subjects with known EGFR, ALK, ROS, BRAF, tropomyosin receptor kinase (TRK), or other actionable mutations are not eligible.
  - Must have had prior platinum-based chemotherapy;
  - No more than 1 prior line of cytotoxic chemotherapy for their advanced disease;
  - Must have received prior anti-PD(L)1 therapy, unless contraindicated;
  - Mixed tumors will be categorized by the predominant cell type. Subject is ineligible if the subject has predominantly squamous cell histology NSCLC or if small cell elements are present.

- Cohort 4, HNSCC (Part A and Part B):
  - Must have pathologically-documented squamous cell carcinoma of the head and neck with primary tumor site arising from the oral cavity, oropharynx, hypopharynx, and larynx; tumors arising from the nasopharynx are excluded.
  - Must have unresectable locally recurrent or metastatic disease;
  - Must have disease progression during or following prior line of systemic therapy;
    - Disease progression after treatment with a platinum-containing regimen for recurrent (disease not amenable to curative treatment)/metastatic disease; or

        - Recurrence/progression within 6 months of last dose of platinum therapy given as part of multimodal therapy in the curative setting (eg locally advanced stage)
    - No more than 1 line of cytotoxic chemotherapy for their advanced disease;
    - May have received prior anti-PD(L)1 therapy, unless contraindicated.
- Cohort 5, esophageal-squamous (Part A and Part B):
    - Must have pathologically-documented squamous cell carcinoma of the esophagus;
    - Must have unresectable locally advanced or metastatic disease;
    - Must have disease progression during or following systemic therapy;
    - Must have had prior platinum-based chemotherapy;
    - No more than 1 line of cytotoxic chemotherapy for their advanced disease.
- Cohort 6, gastric and GEJ adenocarcinoma (Part A and Part B):
    - Must have pathologically-documented gastric or GEJ adenocarcinoma;
    - Must have unresectable locally advanced or metastatic disease;
    - Must have received prior platinum-based therapy;
    - Must have disease progression during or following systemic therapy;
    - Subjects with known human epidermal growth factor receptor 2 (HER2) overexpression must have received prior HER2-targeted therapy;
    - No more than 1 line of prior cytotoxic chemotherapy for their advanced disease;
    - Subjects may have received prior anti-PD(L)1 therapy, unless contraindicated.
- Cohort 7, CRPC (Part B only):
    - Must have histologically or cytologically confirmed adenocarcinoma of the prostate:
        - Subjects with components of small cell or neuroendocrine histology are excluded.
    - Must have metastatic castration-resistant disease:
        - Castration-resistant is defined as progressive disease following adequate medical or surgical (bilateral orchiectomy) castration and testosterone <50 ng/dL (<2.0 nM).
    - Must have been ≥28 days between cessation of androgen receptor-targeted therapy and start of study treatment;
    - Must have received no more than 1 prior line of 2nd generation androgen receptor-targeted therapy (eg, abiraterone acetate, enzalutamide, apalutamide,

or darolutamide) for metastatic castration-sensitive prostate cancer (CSPC) or CRPC;

- No prior cytotoxic chemotherapy in the metastatic CRPC setting:
  - For subjects who received cytotoxic chemotherapy for CSPC, at least 6 months must have elapsed between last dose of chemotherapy and start of study treatment;
  - No more than 1 prior line of cytotoxic chemotherapy for CSPC
- Subjects with measurable and non-measurable disease are eligible if the following criteria are met:
  - A minimum starting PSA level ≥1.0 ng/mL;
  - Subjects with measurable soft tissue disease must have evidence of measurable soft tissue disease according to PCWG3 criteria. Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis to be considered to have progressed;
  - Subjects with nonmeasurable- disease (enrollment after interim analysis and no more than 15 subjects in total) must have documented rising PSA levels or appearance of new lesion according to PCWG3 (Appendix L):
    - PSA progression as defined by 2 increases in PSA level over a previous reference value (a minimum of 3 PSA values total) with an interval of ≥1 week between each assessment where the PSA value at screening should be ≥1 ng/mL, OR
    - Bone disease progression defined by 2 or more new lesions on bone scan
- Subjects with known breast cancer gene (BRCA) mutations are excluded;
- No prior radioisotope therapy or radiotherapy to ≥30% of bone marrow.

- Cohort 8, melanoma (Part B and Part C):
  - Must have histologically or cytologically confirmed cutaneous malignant melanoma;
    - Subjects with mucosal, acral, or uveal melanoma are excluded.
  - Must have locally advanced unresectable or metastatic stage disease;
  - Must have measurable disease:
    - Lesions that have had prior intralesional therapies including talimogene laherparepvec (T-VEC) are not considered measurable;
    - Subjects with metastases limited to the skin (skin-only metastasis) are excluded.
  - Must have progressive disease following anti-PD(L)1 therapy;
  - No prior cytotoxic chemotherapy in the advanced disease setting;

- No more than 2 prior systemic therapies for advanced disease:
  - Adjuvant therapy within 6 months of diagnosis of advanced disease is considered as 1 line of therapy.
  - Prior anti-CTLA4 therapy is allowed;
  - Prior BRAF +/- mitogen-activated protein kinase kinase (MEK) inhibitor therapy:
    - Part B subjects: May have received BRAF +/- MEK inhibitor therapy if BRAF mutated;
    - Part C subjects: Must have received BRAF +/- MEK inhibitor therapy if BRAF mutated

Inclusion criteria for Parts A, B, and C:

1. Measurable disease according to RECIST v1.1 (Appendix H) as assessed by the investigator
   - A minimum of one non-nodal lesion ≥10 mm in the longest diameter from a non-irradiated area
     Or
   - Lymph node lesion ≥15 mm in the shortest diameter from a non-irradiated area
   - If target lesion(s) are located within previously irradiated area only, the subject can be enrolled only if there has been demonstrated progression in the "in field" lesion and upon approval of the sponsor's medical monitor.
2. Age of at least 18 years, or legal age according to local regulations, whichever is older.
3. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (see Appendix J for conversion of performance status using Karnofsky and Lansky scales, if applicable)
4. The following baseline laboratory data:
   - ANC ≥1500/µL assessed at least 2 weeks after growth factor support, if applicable
   - platelet count ≥100 x 10^9/L assessed at least 2 weeks after transfusion with blood products, if applicable
   - hemoglobin (≥8.0 g/dL) assessed at least 2 weeks after transfusion with blood products and/or growth factor support, if applicable
   - serum bilirubin ≤1.5 x upper limit of normal (ULN) or direct bilirubin ≤3 x ULN in subjects diagnosed with Gilbert's syndrome
   - estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable (see Section 7.6.3)
   - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 x ULN (if liver metastases are present, then ≤3 x ULN is allowed)

5. Subjects of childbearing potential as defined in Section 4.3, under the following conditions:
    - 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. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation.
    - Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug administration
    - 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
    - If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix K) 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
6. Subjects who can father children, under the following conditions:
    - 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
    - If sexually active with a subject of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix K) 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
    - If sexually active with a subject who is pregnant or breastfeeding, must consistently use one of 2 contraception options (as defined in Appendix K) 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
7. Available and adequate archival baseline tumor sample is required. If an archival baseline tumor sample is not available, a fresh biopsy sample may be submitted if medically feasible or the medical monitor should be contacted to review this requirement. Formalin fixed paraffin embedded (FFPE) blocks and core needle or excisional biopsy of metastatic site are preferred.
8. The subject or the subject's legally authorized representative must provide written informed consent.

4.2. Exclusion Criteria

Parts A, B, and C

1. Subjects with active concurrent malignancy or a previous malignancy within the past 3 years are excluded. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥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, and does not interfere with the evaluation of the study therapy efficacy or safety.
2. Any anticancer therapy (such as cytotoxic chemotherapy, biologic therapy, immunotherapy etc.) within 3 weeks of starting study treatment. Subjects who are/were on adjuvant hormonal therapy for the treatment of malignancies with negligible risk of metastases (as described in exclusion criteria 1) are eligible.
3. Subjects with known active central nervous system (CNS) lesions (including leptomeningeal metastasis) are excluded. Subjects with symptoms concerning for active CNS disease must have been evaluated and treated per institutional standard of care. Subjects with definitively treated brain metastasis (surgery and/or radiotherapy) are eligible if they meet the following criteria:
   - Asymptomatic from the CNS metastases
   - Completely off steroids; anti-convulsants at a stable dose are allowed.
   - No evidence of clinical and radiographic disease progression in the CNS for ≥3 weeks after definitive radiotherapy and/or surgery
4. Active viral, bacterial, or fungal infection requiring systemic treatment within 7 days prior to the first dose of LV. Routine antimicrobial prophylaxis is permitted.
5. Subjects with any ongoing clinically significant toxicity (Grade 2 or higher, per the NCI CTCAE, v5.0) associated with prior treatment (including systemic therapy, radiotherapy, or surgery) are not permitted (except alopecia).
6. Ongoing sensory or motor neuropathy of Grade ≥2
7. Subjects with known and untreated hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Subjects are eligible if they are on a stable anti-viral treatment or have received curative therapy (check Appendix F for a list of drug-drug interactions).
   - **Part C Arm 2 and Arm 3 only:**
     - HIV+ subjects with a history of Kaposi sarcoma and/or Multicentric Castleman Disease are not eligible.
     - HIV+ subjects on anti-retroviral therapy (ART) must meet the following criteria to be eligible:
       - CD4+ T-cell count >350 cells/mm3 at time of screening
       - Confirmed HIV RNA level below 50 copies/ml or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening

- Stable ART regimen with no changes in drugs or dose modification for at least 4 weeks prior to study entry (Day 1)

8. Current therapy with other systemic antineoplastic or investigational agents
9. Subjects who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 6 months after the final LV administration
10. Known hypersensitivity to any excipient contained in the drug formulation of LV (all Parts) or pembrolizumab (Part C only).
11. 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 (Appendix E).
12. Has received prior radiotherapy within 2 weeks of start of study treatment. A subject is also excluded if radiotherapy occurred more than 2 weeks prior to start of study treatment but the subject has not recovered from radiation-related toxicities, requires corticosteroids, or has had radiation pneumonitis.
13. Other serious or uncontrolled underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up (eg, active cardiac disease, active systemic infection, chronic conditions, any psychiatric or substance abuse disorders), interfere with the subject's cooperation with the requirements of the trial, place the subject at undue risk of SAE, or make the subject unable to receive sustained therapy
14. Has received a live vaccine within 30 days of the planned start of study therapy. Seasonal influenza vaccines for injection are generally inactivated and are allowed; however, intranasal influenza vaccines (eg, Flu-Mist) are live attenuated vaccines and are not allowed.

Part C Only

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg CTLA-4, OX 40, CD137), and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).
16. 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 (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
17. Has had an allogenic tissue/solid organ transplant.
18. History of interstitial lung disease.
19. Current pneumonitis, or history of (non-infectious, including radiation induced) pneumonitis that required steroids.

20. 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.

4.3. Childbearing Potential

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

A subject who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

4.4. Removal of Subjects From Therapy or Assessment

Seagen Inc. or their designee must be notified if a subject is discontinued from study treatment or withdrawn from the study. The reason(s) for discontinuation/withdrawal must be documented in the subject's medical records.

4.4.1. Discontinuation of Study Treatment

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

- Progressive disease (PD)
- AE
- Pregnancy
- Investigator decision
- Subject decision, non-AE
  Note: Ensure that subjects who decide to stop treatment **because of an AE** are not included in this rationale.
- Study or cohort termination by sponsor
- Other, non-AE

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

For Part C Arm 2 and Arm 3:

Patients who discontinue pembrolizumab may continue to receive LV with medical monitor approval. Similarly, patients that discontinue LV may continue to receive pembrolizumab with medical monitor approval. See Sections 5.2.4.3 and 5.3 for details.

Administration of pembrolizumab is limited to 35 cycles (approximately 2 years). The number of administrations is calculated starting with the first dose of pembrolizumab.

4.4.2. Subject Withdrawal From Study

Any subject may be withdrawn from the study for any of the following reasons:

- Subject withdrawal of consent
- Study or cohort termination by sponsor
- Lost to follow-up
- Death
- Other

5. TREATMENTS

5.1. Treatments Administered

Part A (q3wk dosing): LV will be administered at a dose of 2.5 mg/kg as a 30-minute IV infusion on Day 1 of each 21-day cycle. For subjects weighing more than 100 kg, dosing will be capped at 250 mg per infusion. Any subject receiving >200 mg LV per infusion (weight >80 kg) is required to receive prophylactic G-CSF.

Part B (q1wk dosing): LV will be administered at a dose of 1.0 or 1.25 mg/kg as a 30-minute IV infusion on Day 1, Day 8, and Day 15 of each 21-day cycle. The maximum dose will be 200 mg per infusion.

Part C (LV monotherapy or LV plus pembrolizumab combination): LV will be administered at a dose of 1.5 mg/kg (Arms 1 and 2) as a 30-minute IV infusion on Day 1 and Day 8 but not Day 15 of each 21-day cycle (2q3wk). The maximum dose will be 200 mg per infusion. For Arm 3, LV will be administered at a dose of 1.25 mg/kg as a 30-minute IV infusion on Day 1, Day 8, and Day 15 of each 21-day cycle (q1wk). The maximum dose will be 200 mg per infusion. For Arm 2 and Arm 3, pembrolizumab will be administered at a dose of 200 mg approximately 60–90 minutes after LV as a 30-minute IV infusion on Day 1 of each 21-day cycle (q3wk).

5.2. Investigational Study Drug: LV

Detailed information describing the preparation, administration, and storage of LV is located in the 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 Inc. 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) grade or equivalent, 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 grade or equivalent, for IV administration.

5.2.2. Method of Procurement

LV will be provided by the sponsor or designee.

5.2.3. Dose and Administration

LV is administered by IV infusion given over approximately 30 minutes. LV must not be administered as an IV push or bolus. In the absence of infusion-related reactions (IRR), the infusion rate for all subjects 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 can be administered via central venous access line (preferred) or peripheral IV. Clinical site staff should monitor the infusion site closely for redness, swelling, pain, and infection during and at any time after administration. Advise subjects to report redness or discomfort promptly at the time of administration or after infusion. The IV bag containing LV should not be mixed with other medications.

Dosing is based on the subject's actual body weight at the beginning of each cycle.

Detailed instructions for dose preparation are provided in the Pharmacy Instructions.

Part A (q3wk dosing): LV at a dose of 2.5 mg/kg (maximum dose of 250 mg per infusion) will be administered on Day 1 of each 21-day cycle by IV infusion given over approximately 30 minutes. **For subjects weighing greater than 100 kg, dose calculations will be based on 100 kg for these individuals (including dose reductions).** Rounding is permissible within 1 mg of nominal dose. Any subject receiving >200 mg LV per infusion (weight >80 kg) is required to receive prophylactic G-CSF.

Part B (q1wk dosing): LV at a dose of 1.0 or 1.25 mg/kg will be administered on Day 1, Day 8, and Day 15 of each 21-day cycle. The maximum dose will be 200 mg per infusion.

Part C (2q3wk or q1wk dosing): LV at a dose of 1.5 mg/kg will be administered on Day 1 and Day 8 but not Day 15 of each 21-day cycle (2q3wk) for Arm 1 and Arm 2. LV at a dose of 1.25 mg/kg will be administered on Day 1, Day 8, and Day 15 of each 21-day cycle (q1wk) for Arm 3. The maximum dose of LV for all 3 arms will be 200 mg per infusion. For Arm 2 and Arm 3, pembrolizumab infusion must start approximately 60–90 minutes after administration of LV (see Section 5.3.3).

5.2.3.1. Dosing Criteria

The following laboratory criteria must be met on Day 1 of each cycle prior to LV administration:

- Neutrophil count ≥1000/µL (≤ Grade 2)
- Aspartate aminotransferase ≤ Grade 2
- ALT ≤ Grade 2
- Total bilirubin ≤ Grade 2

In Part B and C, neutrophil count must be ≥1000/µL (≤ Grade 2) prior to LV administration on Day 8 and Day 15 (if receiving q1wk dosing) of each cycle.

If the above criteria are not met on the day of dosing, hold the LV dose until the criteria are met. In addition, hold LV dosing for subjects with ≥ Grade 2 peripheral neuropathy (see Table 10).

5.2.4. Dose Modifications

5.2.4.1. Part A (q3wk dosing)

Dose modification guidelines for LV q3wk treatment-associated toxicity are described in Table 9. The maximum doses after modifications are:

- 200 mg for subjects reduced to 2.0 mg/kg
- 150 mg for subjects reduced to 1.5 mg/kg

Table 9: Q3wk LV dose levels

Dose Level	Dose	Maximum Dose
Starting dose	2.5 mg/kg	250 mg
–1	2.0 mg/kg	200 mg
–2	1.5 mg/kg	150 mg

Table 10 describes dose modifications for LV treatment-associated toxicity.

Doses reduced for LV-related toxicity should not be re-escalated.

If a subject has a clinically significant, unresolved AE on Day 1 of C2 or beyond, 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 a subject is unable to tolerate their dose level, additional treatment cycles (C2 or later) may be administered at a lower dose level upon approval by the medical monitor.

Table 10: Dose modifications for LV-associated toxicity (Part A; q3wk dosing)

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
Non-hematologic[a] (except peripheral neuropathy and hyperglycemia)	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 G-CSF support**, then resume treatment at the same dose level. **Prophylactic G-CSF support should be strongly considered for subsequent cycles.** (See Appendix G)	Withhold until toxicity resolves to ≤ Grade 2 or baseline[d,e]. **For neutropenia, strongly consider G-CSF support**, then resume treatment at the same dose level. **Prophylactic G-CSF support is required for all subsequent cycles.** If Grade 4 neutropenia recurs despite G-CSF support, consider dose reduction to dose level –1 or discontinuation. (Appendix G)
Febrile neutropenia[a]			**G-CSF 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 G-CSF is required for all subsequent cycles.** If febrile neutropenia recurs despite G-CSF factor support, consider dose reduction to dose level –1 or discontinuation.	
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 5.6 for detail).			

Note: For subjects weighing ≥100 kg, dosing will be based on 100 kg for these individuals with a maximum calculated dose of 250 mg per infusion when dosed at 2.5 mg/kg.

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

b Subjects 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 subjects who experience Grade 4 infusion-related reactions

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

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

5.2.4.2. Part B (q1wk dosing) and Part C (Arm 3; q1wk dosing)

In the event of an AE or lab criteria that prevents dosing of LV (see Section 5.2.3.1), the LV dose for the week should be withheld. 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 the following week (eg, if the Day 8 dose is skipped, visits will resume on Day 15; if Day 8 and Day 15 doses are skipped, visits will resume of Day 1 of the following cycle). Day 1 of a cycle may be delayed but not skipped.

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 B and Part C (Arm 3) are shown in Table 11.

For Part C (Arm 3), subjects who discontinue pembrolizumab due to a pembrolizumab-related AE (see Section 5.3.4) may continue LV. Similarly, subjects who discontinue LV for a LV-related AE may continue pembrolizumab. See Section 5.5.3 for details on managing overlapping AEs.

Table 11: Q1wk LV dose reductions

Starting Dose	First Dose Reduction (mg/kg/wk)	Second Dose Reduction (mg/kg/wk)
Starting dose 1.0 mg/kg/wk	0.75	0.5
Starting dose 1.25 mg/kg/wk	1.0	0.75

For nonclinical events requiring alteration in dosing schedule (eg, holidays, scheduling conflicts), a +2 day dosing window is allowed. Nonclinical events that require skipping a dose(s), must be approved by sponsor medical monitor. At least 7 days must elapse between each administration of LV.

Dose modification guidelines for LV q1wk treatment-associated toxicity are detailed in Table 12.

Table 12: Dose modifications for LV treatment-associated toxicity (Part B and Part C [Arm 3] q1wk dosing)

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 11)	Withhold until toxicity resolves to ≤ Grade 1, then resume treatment at the next lower dose level (see Table 11)	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 5.6 for details).			
Non-hematologic[a] (except peripheral neuropathy and hyperglycemia)	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 11) 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 5.4.2 and 5.4.3 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 11) 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 11) if treatment is resumed, or discontinue at the discretion of the investigator. See Sections 5.4.2 and 5.4.3 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 11). 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 11) if treatment is resumed, or discontinue at the discretion of the investigator. See Sections 5.4.2 and 5.4.3 on allowed concomitant therapy and myeloid growth factors.	

The maximum dose will be 200 mg per infusion for subjects enrolled in Part B and Part C (Arm 3).

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 Subjects 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 subjects who experience Grade 4 infusion-related reactions.
d Support with blood product transfusions allowed per institutional standard of care.
e Subjects who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.4.3. Part C (Arm 1 and Arm 2; 2q3wk dosing)

In the event of an AE or lab criterion that prevents dosing of LV (see Section 7.6.1), the LV dose should be withheld until the dosing criteria are met. If the Day 1 dose is held, the Day 8 dose should not be given until 7 days later.

In the event of an AE or lab criterion that prevents dosing of LV on Day 8 during the cycle (see Section 7.6.1), the LV dose for the week may be withheld up to 4 days for Arm 1 and Arm 2. 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). Day 1 of a cycle may be delayed but not skipped.

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 (Arms 1 and 2) are shown in Table 13 .

For Arm 2, subjects who discontinue pembrolizumab due to a pembrolizumab-related AE (see Section 5.3.4) may continue LV. Similarly, subjects who discontinue LV for a LV-related AE may continue pembrolizumab. See Section 5.5.3 for details on managing overlapping AEs.

Dose modification guidelines for LV 2q3wk treatment-associated toxicity are described in Table 13 (Arm 1 and Arm 2).

Table 13: 2q3wk LV dose levels

Starting dose	First dose reduction	Second dose reduction[a]
1.5 mg/kg	1.25 mg/kg	1.0 mg/kg[b]

[a] 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.
[b] The dose may be reduced to 0.75 mg/kg following approval from the medical monitor.

For nonclinical events requiring alteration in dosing schedule (eg, 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 14 describes dose modifications for LV treatment-associated toxicity for the 2q3wk schedule (Arm 1 and Arm 2).

Doses reduced for LV-related toxicity should not be re-escalated.

If a subject has a clinically significant, unresolved AE on Day 1 of C2 or beyond, 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 a subject is unable to tolerate their dose level, additional treatment cycles (C2 or later) may be administered at a lower dose level upon approval by the medical monitor.

Table 14: Dose modifications for LV-associated toxicity (Part C [Arms 1 and 2]; 2q3wk dosing)

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 (see Table 13)	Withhold until toxicity resolves to ≤ Grade 1, then resume treatment at the next lower dose level (see Table 13)	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 5.6 for detail).			
Non-hematologic[a] (except peripheral neuropathy and hyperglycemia)	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 13) 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 G-CSF support**, then resume treatment at the same dose level. **Prophylactic G-CSF support should be strongly considered for subsequent cycles.** (See Appendix G)	Withhold until toxicity resolves to ≤ Grade 2 or baseline[d,e]. **For neutropenia, strongly consider G-CSF support**, then resume treatment at the same dose level. **Prophylactic G-CSF support is <u>required</u> for all subsequent cycles.** If Grade 4 neutropenia recurs despite G-CSF support, consider dose reduction to dose level –1 (see Table 13) or discontinuation. (Appendix G)
Febrile neutropenia[a]			**G-CSF 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 G-CSF is required for all subsequent cycles.** If febrile neutropenia recurs despite G-CSF factor support, consider dose reduction to dose level –1 (see Table 13) or discontinuation.	

The maximum dose will be 200 mg per infusion for patients enrolled in Part C.

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 Subjects 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 subjects who experience Grade 4 infusion-related reactions.

d Support with blood product transfusions allowed per institutional standard of care.
e Subjects who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.5. Storage and Handling

Single-use vials containing LV must be stored under refrigeration set at 2–8 °C in an appropriate locked room 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 set 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 conditions.

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 or designee.

Specific instructions for the preparation, handling, storage, and accountability are found in the Pharmacy Manual.

5.2.6. Packaging and Labeling

LV is supplied in single-use glass vials. The drug product vials are labeled as SGN-LIV1A, the compound code.

5.2.7. 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 instructions for dose preparation are provided in the Pharmacy Instructions.

5.3. Pembrolizumab

Patients will receive pembrolizumab 200 mg in combination with LV.

5.3.1. Description

Pembrolizumab (MK-3475) 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 6.4 and Appendix D.

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. Dose Modifications

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These 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 15.

Table 15 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 (CTCAE v5.0)	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[a]	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)

Immune-related AEs	Toxicity grade or conditions (CTCAE v5.0)	Action with pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg 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[d]	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	Monitor subjects 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 [d]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2–4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	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		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

Immune-related AEs	Toxicity grade or conditions (CTCAE v5.0)	Action with pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
	clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)			
	Grade 2, 3, or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)= adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=Type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

NOTE: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline if baseline abnormal; bilirubin: >1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline if baseline abnormal; bilirubin: >3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN if baseline normal; >20.0 x baseline if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] 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.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

5.3.4.2. 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 16.

Table 16 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 (eg, 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 (eg, 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).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal	**Stop Infusion**. Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
impairment, pulmonary infiltrates)	• Pressors • Corticosteroids	
Grade 4: Life-threatening; pressor or ventilator support indicated	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. Subject 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 v5.0 (CTCAE) at http://ctep.cancer.gov

5.3.4.3. Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or unforeseen circumstances not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, 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 (see Sections 5.2.4.2 and 5.2.4.3) 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).

5.3.5. Storage and Handling

Pembrolizumab should be stored and handled per the pharmacy manual.

5.3.6. Packaging and Labeling

Pembrolizumab is commercially available in the US.

5.3.7. Preparation

Pembrolizumab should be prepared per the pharmacy manual.

5.4. 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.

5.4.1. Required Concomitant Therapy

G-CSF is required in the following situations.

- Part A: Subjects who experience Grade 4 neutropenia or febrile neutropenia (any grade) in any cycle with LV treatment must receive G-CSF treatment during the cycle, and must receive prophylactic G-CSF for all subsequent cycles.
- Part A: Subjects weighing over 80 kg and receiving >200 mg per infusion of LV in a cycle must be given prophylactic G-CSF, starting with their first dose of >200 mg per infusion. Once a subject receives G-CSF, it is strongly recommended that G-CSF continue to be administered to that subject at each subsequent cycle, regardless of weight change or LV dose, if it is deemed to be needed per investigator's clinical judgment.
- In Part B and Part C, primary prophylactic G-CSF is not required but is allowed (see Section 5.4.2 Allowed Concomitant Therapy and Section 5.4.3. Myeloid Growth Factors).

The administration of G-CSF should be consistent with American Society of Clinical Oncology (ASCO) guidelines (Smith 2015) (Appendix G).

- Prophylactic G-CSF should start 1 to 3 days after LV administration.
- G-CSF (including pegfilgrastim) should not be given within 24 hours prior to the dose of LV.
- If pegfilgrastim is used, a one-time dose per cycle is recommended.
- If daily G-CSF for treatment of AEs is used, treat for at least 5 to 7 days, or until the ANC is >1000/mm^3 (≤ Grade 2).

If the subject 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 subject should continue suppressive or prophylactic anti-infectives for the duration of study participation.

5.4.2. Allowed Concomitant Therapy

The use of antibiotics including prophylactics, when applicable, is allowed. Subjects 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 Prescribing Information, Seagen, Inc., Oct 2019), 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. See Appendix F for a list of P-gp and CYP3A inducers and inhibitors.

Therapy with bisphosphonates or other fracture prophylaxis agents are permitted.

5.4.2.1. Blood Product Transfusions

Transfusions of blood products may be administered according to institutional standards.

5.4.2.2. Premedication

Routine premedication for infusion reactions should not be administered prior to the first dose of LV. However, subjects who experience IRRs may receive subsequent treatment with premedication. The use of intermittent high-dose corticosteroid treatment of >20 mg/day to prevent or manage hypersensitivity reactions, or other noncancer related symptoms, is allowed. For the management of infusion reactions, including recommended concomitant therapy, see Section 5.5.1.

5.4.2.3. Radiotherapy

Palliative radiotherapy (eg, treatment for stable symptomatic, non-target solitary lesion) may be considered on an exceptional case-by-case basis after consultation with the medical monitor, provided it does not interfere with assessment of tumor response per RECIST v1.1, put the subject 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.

5.4.2.4. Supportive Care Medications

It is recommended that subjects receive treatment for constipation, nausea, vomiting, or other gastrointestinal signs or symptoms.

Although not required, subjects should be up-to-date on any recommended vaccinations prior to study entry. Seasonal inactivated (non-live) influenza vaccine is allowed.

5.4.3. Myeloid Growth Factors

See Section 5.4.1 and Appendix G. Subjects in any cohort of the study may receive G-CSF as clinically indicated.

Myeloid growth factors (including pegfilgrastim) **should not be given** within 24 hours prior to any dose of LV.

For subjects enrolled in Part B and C, long-acting myeloid growth factors (such as pegfilgrastim) may not be appropriate when LV is given weekly. 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. In addition, adherence to the 2015 ASCO guideline for the use of white blood cell growth factors is recommended for the management and/or prophylaxis of neutropenia and febrile neutropenia (Smith 2015).

5.4.4. Prohibited Concomitant Therapy

No other investigational drug, immunosuppressive medication, non-study systemic antineoplastic therapy, or approved anticancer treatment is permitted during the treatment period, including chemotherapy, endocrine therapy, biological response modifiers, surgery, immunotherapy, or radiotherapy (except palliative radiotherapy, see Section 5.4.2.3). Concurrent participation in another clinical trial of a medical intervention is not allowed.

5.4.4.1. Prohibited Concomitant Therapy for Pembrolizumab (Part C)

Systemic glucocorticoids are prohibited for any purpose other than the following:

- To modulate symptoms from an event of clinical interest of suspected immunologic etiology
- As supportive care during transfusion or administration of G-CSF (Section 5.4.2.2).
- For the prevention of emesis
- To premedicate for IV contrast allergies
- To treat chronic obstructive pulmonary disease (COPD) exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone or equivalent)
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or COPD

The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

5.5. Management of Adverse Reactions

5.5.1. Management of Infusion Reactions

5.5.1.1. 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 subject 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.

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

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

Premedication for LV may include acetaminophen (or equivalent, eg, paracetamol), 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 should be immediately and permanently discontinued.

See Section 7.6.1.2 for details regarding recording AEs of infusion reactions.

5.5.1.2. Pembrolizumab

Details on IRRs for pembrolizumab are detailed in Section 5.3.4.2 and Table 16.

See Section 7.6.1.2 for details regarding recording AEs of infusion reactions.

5.5.1.3. 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.

5.5.2. Management of Overdose

5.5.2.1. LV Overdose

In the event of an overdose of LV >10%, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. The subject 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 G-CSF is strongly recommended for the management of neutropenia and febrile neutropenia (Smith 2015). There is currently no known antidote for an overdose of LV.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of LV administered, subject weight) and AEs, if any.

5.5.2.2. Pembrolizumab 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.

5.5.3. Management of Overlapping Toxicities

The IBs for LV and pembrolizumab individually describe AEs commonly observed relative to individual study treatments, 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.

5.5.4. 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 5.3.4. 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 5.3.4 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.

5.6. 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, subjects should be treated according to local standard of care and referral to endocrinology may be considered.

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

Subjects who enter the study with elevated hemoglobin A1c (HbA1c) (≥6.5%) or fasting glucose (≥126 mg/dL or ≥7 mmol/L) at screening should receive glucose management prior to or within 1 week of starting study treatment.

Blood glucose may be measured by blood glucose meter or laboratory-performed blood glucose test.

- Part A: random blood glucose should be checked prior to dosing on Day 1 of each 21-day cycle.
- Part B: random blood glucose should be checked prior to dosing on Days 1, 8, and 15 of the first 2 cycles. For Cycle 3 and later, blood glucose should be checked on Day 1 of each cycle, and may be checked on Day 8 and/or Day 15 if clinically indicated for subjects at risk of hyperglycemia.
- Part C: random blood glucose should be checked prior to dosing on each dosing day of the first 2 cycles. For Cycle 3 and later, blood glucose should be checked on Day 1 of each cycle, and may be checked on Day 8 and/or Day 15 if clinically indicated for subjects at risk of hyperglycemia.

Parts A, B, and C: If blood glucose is >250 mg/dL or >13.9 mmol/L, testing may be repeated on same day of dosing. LV dose may be delivered on the same day when blood glucose has decreased to 250 mg/dL or lower and the subject is clinically and metabolically stable. LV should be withheld if repeated blood glucose is >250 mg/dL or >13.9 mmol/L (non-fasting or fasting).

Note: For AE reporting purposes, the severity of hyperglycemia in the NCI CTCAE, version 5, is graded by the medical management required to address hyperglycemia and not by the value of glucose measurement.

5.7. Treatment Compliance

IV administration of LV will be performed by study site staff and documented in source documents and the case report form (CRF).

For Part C, IV administration of pembrolizumab will be performed by study site staff and documented in source documents and the CRF.

6. STUDY ACTIVITIES

6.1. Schedule of Events

A schedule of events is provided in Appendix A for baseline/screening and in Appendix B, Appendix C, and Appendix D for treatment. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7. AEs and concomitant medications will be recorded from Day 1 (predose) through the safety-reporting period (end of treatment [EOT] visit or 30 days after the last study treatment, whichever is later, with the exception of AEs of interest, which will be followed until resolution, death, or withdrawal of consent; see Section 7.6.1.3). Any study protocol-related AE (defined in Section 7.6.1.1) as well as any concomitant medications given for the treatment of the AE, should be recorded from the time of informed consent.

6.2. Part A (q3wk dosing)

6.2.1. Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- CT or MRI scans (CT/MRI) (see Section 7.2)
- Brain CT or brain MRI
- Confirm availability of adequate archival tumor sample for all subjects, if not available, a fresh biopsy may be collected if medically feasible (see Section 7.1.2 for details of requirements).
- HbA1c and fasting blood glucose (see Section 7.6.3). If HbA1c or fasting glucose is elevated with confirmation upon repeat testing (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL or ≥7 mmol/L), the subject should receive glucose management before Cycle 1 (C1) Day 1 or within the first week of C1 (results to be submitted to ICON Results Integration Services [iRIS]).

6.2.2. Baseline Visit (Days –7 to Day 1)

- Physical exam (Section 7.6.4), including height and weight. Measurements of height obtained within the previous 12 months may be used.
- Vital signs (Section 7.6.2)
- Pregnancy test for subjects of childbearing potential (serum or urine pregnancy test; see Section 7.6.5) – must be performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)
- Complete blood count (CBC) with differential (see Section 7.6.3; results to be submitted to iRIS)

- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- Estimated GFR calculation (see Section 7.6.3; results to be submitted to iRIS)
- Collection of concomitant medication information
- Collection of AEs

6.2.3. Treatment Cycle (Day 1 to Day 21)

6.2.3.1. Day 1

If baseline visit activities occur within 3 days prior to C1 Day 1, the following assessments do not need to be repeated at the C1 Day 1 visit:

- Physical exam (Section 7.6.4) including weight
- ECOG performance status (Appendix J)
- CBC with differential
- Serum chemistry panel and liver function tests
- Pregnancy test

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (Section 7.6.4), including weight
- Pregnancy test (serum or urine) for subjects of childbearing potential (see Section 7.6.5) – does not need to be repeated if it has been performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)
- Random blood glucose to be collected predose on the day of LV administration (see Section 5.6; results to be submitted to iRIS)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK and antitherapeutic antibody (ATA) assessment (C1-Cycle 5 [C5] and every 5 cycles thereafter, see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 to C6 only; see Section 7.4.1)
- CT/MRI, if required: It is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

- LV administration (within ± 2 days from Day 21 of the previous cycle; see Section 5.2.3)

Postdose

- Blood samples for postdose PK assessment (C1-C5 and every 5 cycles thereafter, see Section 7.3 for time points)
- Vital signs (within 30 minutes of ending each infusion, and during infusion as clinically indicated see Section 7.6.2)
- If available, submit tumor tissue samples for biomarker analysis as soon as reasonably possible after the subject has met all eligibility requirements (C1 only; see Section 7.4.2)

6.2.3.2. Day 3

- For subjects who receive >200 mg LV per infusion, start mandatory prophylactic G-CSF administration (may begin on Days 2, 3, or 4; see Section 5.4.1)
    - Other subjects who are to receive prophylactic G-CSF should start G-CSF (may begin on Days 2, 3, or 4)
- Blood samples for PK assessment (visit window may be +1 day; C1 and Cycle 4 [C4] only, see Section 7.3)

6.2.3.3. Day 8 (± 2 days)

- Physical exam (C1 only; see Section 7.6.4)
- CBC with differential (C1 and C2 only; see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (C1 and C2 only; see Section 7.6.3; results to be submitted to iRIS)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 and Table 17 for time points)

6.2.3.4. Day 15 (± 2 days)

- Physical exam (C1 only; see Section 7.6.4)
- CBC with differential (C1 and C2 only; see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (C1 and C2 only; see Section 7.6.3; results to be submitted to iRIS)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 and C2 only; see Section 7.4.1)

6.3. Part B (q1wk dosing)

6.3.1. Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- For prostate cancer subjects:
  - Bone scan (see Section 7.2.1)
  - PSA test (see Section 7.6.3)
  - Testosterone measurement (see Section 7.6.3; results to be submitted to iRIS)
- CT/MRI (see Section 7.2)
- Brain CT or brain MRI
- Confirm availability of adequate archival tumor sample for all subjects, if not available, a fresh biopsy may be collected if medically feasible (see Section 7.1.2 for details of requirements).
- HbA1c and fasting blood glucose (see Section 7.6.3). If HbA1c or fasting glucose is elevated with confirmation upon repeat testing (HbA1c ≥6.5%, fasting glucose ≥126 mg/dL or ≥7 mmol/L), the subject should receive glucose management before C1 Day 1 or within the first week of C1 (results to be submitted to iRIS).

6.3.2. Baseline Visit (Days –7 to Day 1)

- Physical exam (Section 7.6.4), including height and weight. Measurements of height obtained within the previous 12 months may be used.
- Vital signs (Section 7.6.2)
- Pregnancy test for subjects of childbearing potential (serum or urine pregnancy test; see Section 7.6.5) – must be performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- Estimated GFR calculation (see Section 7.6.3; results to be submitted to iRIS)
- Collection of concomitant medication information
- Collection of AEs

6.3.3. Treatment Cycle (Day 1 to Day 21)

6.3.3.1. Day 1

If baseline visit activities occur within 3 days prior to C1 Day 1, the following assessments do not need to be repeated at the C1 Day 1 visit:

- Physical exam (Section 7.6.4) including weight
- ECOG performance status (Appendix J)
- CBC with differential
- Serum chemistry panel and liver function tests
- Pregnancy test
- PSA test for prostate cancer subjects

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (Section 7.6.4), including weight
- Pregnancy test (serum or urine) for subjects of childbearing potential (see Section 7.6.5) – does not need to be repeated if it has been performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)
- Random blood glucose to be collected prior to dosing on Day 1 of each 21-day cycle (see Section 5.6; results to be submitted to iRIS)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK and ATA assessment (C1-C5 and every 5 cycles thereafter, see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 to C6 only; see Section 7.4.1)
- Review CT/MRI, if applicable (see Section 7.2)
- For prostate cancer subjects:
    - Review bone scan, if applicable (see Section 7.2)
    - PSA test (see Section 7.6.3)
- LV administration (a +2 day dosing window is allowed for subsequent dosing within a cycle; see Section 5.2.3). For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.

Postdose

- Blood samples for postdose PK assessment (C1-C5 and every 5 cycles thereafter, see Section 7.3 for time points)
- Vital signs (within 30 minutes of ending each infusion, and during infusion as clinically indicated; see Section 7.6.2)
- If available, submit tumor tissue samples for biomarker analysis as soon as reasonably possible after the subject has met all eligibility requirements (C1 only; see Section 7.4.2)

6.3.3.2. Day 3

- Blood samples for PK assessment (visit window may be +1 day; C1 and C4 only, see Section 7.3)

6.3.3.3. Day 8 (± 2 days)

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (Section 7.6.4) (C1 only)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Random blood glucose in Cycles 1 and 2. Following C2, random blood glucose may be collected as indicated in subjects at risk for hyperglycemia. (see Section 5.6; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)
- LV administration (a +2 day dosing window is allowed for subsequent dosing within a cycle; see Section 5.2.3). For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.

Postdose

- Vital signs (within 30 minutes of ending each infusion, and during infusion as clinically indicated; see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)

6.3.3.4. Day 15 (± 2 days)

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (C1 only; see Section 7.6.4)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Random blood glucose in Cycles 1 and 2. Following C2, random blood glucose may be collected as indicated in subjects at risk for hyperglycemia. (see Section 5.6; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 and C2 only; see Section 7.4.1)
- LV administration (a +2 day dosing window is allowed for subsequent dosing within a cycle; see Section 5.2.3). For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.

Postdose

- Vital signs (within 30 minutes of ending each infusion, and during infusion as clinically indicated; see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)

6.4. Part C (monotherapy and pembrolizumab combination)

6.4.1. Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- CT/MRI (see Section 7.2)
- Brain CT or brain MRI
- Confirm availability of adequate archival tumor sample for all subjects, if not available, a fresh biopsy may be collected if medically feasible (see Section 7.1.2 for details of requirements).
- HbA1c and fasting blood glucose (see Section 7.6.3). If HbA1c or fasting glucose is elevated with confirmation upon repeat testing (HbA1c ≥6.5%, fasting glucose

≥126 mg/dL or ≥7 mmol/L), the subject should receive glucose management before C1 Day 1 or within the first week of C1 (results to be submitted to iRIS).

- **Arm 2 and Arm 3**: Thyroid function test (detailed in Section 7.6.3).

6.4.2. Baseline Visit (Days –7 to Day 1)

- Physical exam (Section 7.6.4), including height and weight. Measurements of height obtained within the previous 12 months may be used.
- Vital signs (Section 7.6.2)
- Pregnancy test for subjects of childbearing potential (serum or urine pregnancy test; see Section 7.6.5) – must be performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- Estimated GFR calculation (see Section 7.6.3; results to be submitted to iRIS)
- Collection of concomitant medication information
- Collection of AEs

6.4.3. Treatment Cycle (Day 1 to Day 21)

6.4.3.1. Day 1

If baseline visit activities occur within 3 days prior to C1 Day 1, the following assessments do not need to be repeated at the C1 Day 1 visit:

- Physical exam (Section 7.6.4) including weight
- ECOG performance status (Appendix J)
- CBC with differential
- Serum chemistry panel and liver function tests
- Pregnancy test

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (Section 7.6.4), including weight
- Pregnancy test (serum or urine) for subjects of childbearing potential (see Section 7.6.5) – does not need to be repeated if it has been performed within 3 days prior to administration of LV
- ECOG performance status (Appendix J)

- Random blood glucose to be collected prior to dosing on Day 1 of each 21-day cycle (see Section 5.6; results to be submitted to iRIS)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- **Arm 2 and Arm 3**: Thyroid function tests (detailed in Section 7.6.3); to include thyroid-stimulating hormone (TSH), T3 or free T3, and free T4). Day 1 of each odd-numbered cycle only (i.e. Cycles 1, 3, 5, 7, etc).
- Vital signs:
    - **Arm 1**: within 60 minutes prior to the start of LV infusion, see Section 7.6.2
    - **Arm 2 and Arm 3**: within 60 minutes prior to LV infusion, within 60 minutes prior to pembrolizumab infusion, see Section 7.6.2
- Blood samples for PK and ATA assessment (C1 to C5 and every 5 cycles thereafter, see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 to C6 only; see Section 7.4.1)
- Review CT/MRI, if applicable (see Section 7.2)
- **Arm 1, Arm 2, and Arm 3**: LV administration (a +4 day dosing window for Arm 1 and Arm 2 and a +2 day window for Arm 3) is allowed for subsequent dosing within a cycle; see Sections 5.2.3, 5.2.4.2, and 5.2.4.3. For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.
- **Arm 2 and Arm 3**: Pembrolizumab will be administered 60–90 minutes following LV. For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor.

Postdose

- Vital signs:
    - **Arm 1:** within 30 minutes of ending each LV infusion, and during infusion as clinically indicated; see Section 7.6.2
    - **Arm 2 and Arm 3:** within 2 hours of ending each infusion, and during infusion/s as clinically indicated; see Section 7.6.2
- Blood samples for PK assessment (see Section 7.3 for time points)

6.4.3.2. Day 3

- Blood samples for PK assessment (visit window may be +1 day; C1 and C4 only, see Section 7.3)

6.4.3.3. Day 8 (± 2 days)

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (Section 7.6.4) (C1 only)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Random blood glucose in Cycles 1 and 2. Following Cycle 2, random blood glucose may be collected as indicated in subjects at risk for hyperglycemia. (see Section 5.6; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)
- **Arm 1, Arm 2, and Arm 3**: LV administration (a +4 day dosing window for Arm 1 and Arm 2 and a +2 day window for Arm 3). See Sections 5.2.3, 5.2.4.2, and 5.2.4.3. For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.

Postdose

- Vital signs:
  - **Arm 1**: within 30 minutes of ending each LV infusion, and during infusion as clinically indicated; see Section 7.6.2
  - **Arm 2 and Arm 3**: within 2 hours of ending each infusion, and during infusion/s as clinically indicated; see Section 7.6.2
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)

6.4.3.4. Day 15 (± 2 days)

Note: Subjects in Arm 1 and Arm 2 will require the following:

- CBC with differential (–2-day window; see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Physical exam (C1 only; see Section 7.6.4)

The following is for Arm 3 only:

Predose

- Confirm subject meets dosing criteria (Section 5.2.3.1)
- Physical exam (C1 only; see Section 7.6.4)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS), Cycles 1 and 2 only
- Random blood glucose in Cycles 1 and 2. Following C2, random blood glucose may be collected as indicated in subjects at risk for hyperglycemia. (see Section 5.6; results to be submitted to iRIS)
- Vital signs (within 60 minutes prior to the start of LV infusion, see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)
- Blood samples for biomarker assessment (C1 and C2 only; see Section 7.4.1)
- LV administration (a +2 day dosing window is allowed for subsequent dosing within a cycle; see Sections 5.2.3 and Section 5.2.4.2). For nonclinical events requiring skipping a dose(s), must consult with and obtain approval by sponsor medical monitor. At least 7 days must elapse between administrations of LV.

Postdose

- Vital signs (within 2 hours of ending each infusion, and during infusion(s) as clinically indicated; see Section 7.6.2)
- Blood samples for PK assessment (C1 and C4 only; see Section 7.3 for time points)

6.5. On treatment Response Assessments

Time points for radiographic exams for patients with RECIST v1.1 measurable tumor lesions or bone scan should be calendar based and do not depend on cycle visits. It is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

The schedule of response assessments should not be adjusted for dose delays, dose interruptions, or other reasons for changes in the timing of a subject's study activities. Imaging should be conducted on the following schedule (Sections 6.5.1 and 6.5.2) until treatment is discontinued for any of the following reasons: disease progression, unacceptable toxicity, investigator decision, consent withdrawal, study termination by the sponsor, pregnancy, or death, whichever comes first. For all tumor cohorts, imaging should also be performed whenever disease progression is suspected.

6.5.1. For non-prostate cancer subjects (Cohorts 1–6, and 8):

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

- Every 12 weeks (±7 days) thereafter

Objective responses (CR or PR) will be confirmed with repeat scans 4–6 weeks after the first documentation of response.

6.5.2. For prostate cancer subjects (Cohort 7):

- PSA assessment every 3 weeks (±3 days) per calendar
- CT/MRI scan every 8 weeks (±7 days) per calendar for the first 24 weeks, then every 12 weeks (±7 days) thereafter
- Bone scan every 8 weeks (±7 days) per calendar for the first 24 weeks, then every 12 weeks (±7 days) thereafter

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

Subjects will continue to receive LV until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, study termination by the sponsor, pregnancy, or death, whichever comes first.

Regardless of time since last dose, EOT visits should be completed prior to administration of a new therapy. EOT visits should occur within 30 to 37 days after the last dose of LV unless delayed due to an AE. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the subject's last study treatment to assess for AEs and concomitant medications.

- Physical examination (Section 7.6.4), including weight
- Vital signs (Section 7.6.2)
- Pregnancy test for subjects of childbearing potential (see Section 7.6.5)
- ECOG performance status (Appendix I)
- CBC with differential (see Section 7.6.3; results to be submitted to iRIS)
- HbA1c (see Section 7.6.3; results to be submitted to iRIS)
- Serum chemistry panel and liver function tests (see Section 7.6.3; results to be submitted to iRIS)
- CT/MRI scan (see Section 7.2 for details); not required if previous scan was completed within 4 weeks prior to EOT
- Blood samples for PK and ATA assessment (see Section 7.3 for time points)
- Blood samples for biomarker assessment (see Section 7.4.1)
- For prostate cancer subjects:
    - PSA assessment (see Section 7.6.3)
    - Bone scan (see Section 7.2.1), not required if previous scan was completed within 4 weeks prior to EOT

6.7. Follow-up

All subjects will be followed for survival until death or study closure, whichever occurs first. Survival and subsequent anticancer therapy follow-up may be conducted with clinic visits or telephone calls.

For subjects who discontinue study treatment for reasons other than progression, the following assessments will be conducted every 6 weeks (± 3 days) for 12 months after the first dose of LV and every 12 weeks (± 7 days) thereafter, until disease progression, initiation of a new anticancer therapy, investigator decision, consent withdrawal, study termination by the sponsor, pregnancy, or death, whichever comes first:

- Physical examination (see Section 7.6.4)
- Pregnancy test for subjects of childbearing potential 24 weeks after the last dose of LV (see Section 7.6.5)
- CT/MRI scan (see Section 7.2 for details); after a year of follow-up, reduce frequency to institution's standard of care
- In subjects who discontinue study treatment due to pregnancy, response assessments should be conducted as appropriate

For prostate cancer subjects who discontinue study treatment for reasons other than progression, the following assessments will be conducted until disease progression, initiation of a new anticancer therapy, investigator decision, consent withdrawal, study termination by the sponsor, or death, whichever comes first:

- Physical examination every 12 weeks (±7 days) (see Section 7.6.4)
- PSA assessment every 12 weeks (±7 days)
- Bone scan every 12 weeks (±7 days) (see Section 7.2.1)
- Soft tissue tumor assessment (CT/MRI) every 12 weeks (±7 days) until disease progression for subjects with measurable disease

6.8. End of Study/End of Follow-up

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

If a subject requests to be withdrawn from follow-up, this request must be documented in the source documents. When a subject withdraws consent, the sponsor should be notified as soon as possible. If the subject withdraws from study, the study staff may use a public information source (eg, county records) to obtain information about survival status only.

Three follow-up attempts must be documented in the source documents before a subject is declared lost to follow-up. The sponsor should be notified as soon as possible if this occurs.

The study will be closed 3 years after the last subject receives the last dose, or when no subjects remain in follow-up, whichever occurs first.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

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

Subject 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.

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

For prostate cancer subjects, a bone scan should be performed to assess disease at screening.

Required assessments for all subjects at screening and/or baseline are described in Sections 6.2 and 6.3, Section 7.6, and Appendix A.

7.1.1. Tumor Tissue After Treatment

If a tumor tissue sample is obtained as part of standard of care at any time during the study (until disease progression after treatment with LV), with the subject's consent, a part of that sample or an additional sample obtained during the same procedure may be collected and submitted to the sponsor for biomarker testing.

Biomarker assessments that will be performed using tumor tissue are outlined in Section 7.4.2.

7.1.2. Tumor Sample Requirements and Collection

Tumor tissue samples must be available for submission (see Section 7.4.2).

- Available and adequate archival baseline tumor sample is required. If an archival baseline tumor sample is not available, a fresh biopsy sample may be submitted if medically feasible or the medical monitor should be contacted to review this requirement.
- FFPE blocks are requested. If an FFPE block is not available, 30 unstained slides are required or contact medical monitor for alternative submission possibilities. Core needle or excisional biopsy is preferred. If neither is possible, discuss with medical monitor whether biopsy obtained via alternative methods may be appropriate.
- If a tumor tissue sample is obtained as part of standard of care during the study, a part of that sample is requested to be submitted to the sponsor with the subject's consent.
- Unscheduled tumor biopsies performed while the subject is on study should be made available to the sponsor if feasible and if subject consents to the submission of this tissue. For example, if a biopsy on residual tumor is performed at EOT or at progression, a sample should be sent to sponsor (if available).

7.2. Response/Efficacy Assessments

The determination of antitumor activity will be based on objective response assessments made by the investigator according to the RECIST v1.1 (Appendix H) (Eisenhauer 2009) and treatment

decisions by the investigator will be based on these assessments for Parts A–C (Arm 1 only). For subjects in Part C (Arms 2 and 3), treatment decisions by the investigator will be based on iRECIST (see Appendix I) (Seymour 2017). Clinical response of CR, PR, SD, or PD will be determined at each assessment. In addition, images will be collected by an independent review facility for possible future analysis.

For non-prostate cancer subjects, responses (CR or PR) will be confirmed 4–6 weeks after first documentation of response.

For all subjects, tumor imaging should also be performed whenever disease progression is suspected.

Measures of anticancer activity will be assessed by either CT with contrast or MRI scans at protocol-specified time points. A diagnostic quality CT is required unless medically contraindicated.

For prostate cancer subjects, PSA response is defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. The duration of PSA response is defined as the time between the first evaluation at which the response criteria are met and the first documentation of PSA progression. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint.

For subjects unable to tolerate contrast-enhanced CT assessments, MRI imaging is acceptable. MRI scans may not be appropriate to assess lung parenchymal lesions and CT without contrast enhancement is acceptable in such situations. **Subjects must be evaluated with the 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.

Further details are provided in the study imaging manual.

Tumor assessments will continue until the subject has radiologically-confirmed disease progression per RECIST v1.1 by the investigator according to Sections 6.4, 6.6, and 6.7. Subjects who discontinue study treatment for reasons other than objective disease progression by RECIST v1.1 (see Appendix H) will continue to receive tumor assessments according to Section 6.7.

For Part C Arms 2 and 3, 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 criteria allow for continued treatment beyond apparent progression of disease in order to confirm response (see Appendix I). In patients who have initial evidence of radiological PD per RECIST v1.1 in Part C (Arms 2 and 3), 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 (eg, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued 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.

Subjects' 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.

7.2.1. Tumor Cohort-Specific Imaging Requirements

For subjects with SCLC, NSCLC, gastric, GEJ adenocarcinoma, or melanoma, imaging must include chest, abdomen, and pelvis. Other specific regions of disease involvement should also be imaged.

For subjects with head and neck cancer, imaging of the neck and chest are required. Other specific regions of disease involvement should also be imaged.

For subjects with esophageal squamous cell cancer, imaging of the chest and abdomen are required. Other specific regions of disease involvement should also be imaged.

For subjects with prostate cancer, cross-sectional imaging of the chest, abdomen, pelvis, as well as bone scintigraphy are required. Other specific regions of disease involvement should also be imaged.

7.3. Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ATA assessment will be collected at protocol-specified time points per the schedules provided in Table 17, Table 18, and Table 19. Sensitive, validated immunoassay or liquid chromatography with tandem mass spectrometry (LC/MS/MS) assays, as appropriate, will be used to measure the concentrations of LV (ADC), total antibody, and MMAE in plasma and ATA in serum. Remaining PK samples will be archived for possible analysis of other LV-related species.

For Part C Arms 2 and 3, additional PK and ATA samples will be collected and archived for possible analysis of pembrolizumab concentrations and levels of ATAs to pembrolizumab, respectively.

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

Table 17: Pharmacokinetic, immunogenicity, and biomarker sample collection time points – 21 day cycles (Part A; q3wk dosing)

Cycle	Study Day	Time	Window	Relative Time	PK	ATA	Serum	Plasma	Blood Cell Pellet	Archived tumor specimen	Tumor biopsy (FFPE)
Screening	–28 to 1	N/A	N/A	N/A						X[a]	
1 and 4	Day 1	Pre-dose	within 4 hr[b]	START of infusion	X	X	X	X	X		
		End of infusion	within 15 min	END of infusion	X						
		2 hr	±15 min		X						
		4 hr	±15 min		X						
	Day 3	48 hr	+24 hr	START of infusion	X[c]						
	Day 8	168 hr	±48 hr		X						
	Day 15	336 hr	±48 hr		X		X[d]	X[d]	X[d]		
2	Day 1	Pre-dose	within 4 hr	START of infusion	X	X	X	X	X		
		End of infusion	within 15 min	END of infusion	X						
	Day 15	336 hr	±48 hr	START of infusion			X	X	X		
3, 5, and every 5th cycle thereafter	Day 1	Pre-dose	within 4 hr	START of infusion	X	X	X[e]	X[e]	X[e]		
		End of infusion	within 15 min	END of infusion	X						
6	Day 1	Pre-dose	within 4 hr	START of infusion			X	X	X		
EOT					X	X	X	X			
Additional biopsy											X[a]

a See Section 7.1.2 for details.
b Cycle 1, Day 1 pre-dose window is 24 hours.
c Blood draws at indicated time points may be obtained by a visiting nurse service.
d Draw only for Cycle 1 and Cycle 2.
e Cycle 3 and Cycle 5 only.

Table 18: Pharmacokinetic, immunogenicity, and biomarker sample collection time points – 21 day cycles (Part B; q1wk dosing)

Cycle	Study Day	Time	Window	Relative Time	PK	ATA	Serum	Plasma	Blood Cell Pellet	Archived tumor specimen	Tumor biopsy (FFPE)
Screening	–28 to 1	N/A	N/A	N/A						X[a]	
1 and 4	Day 1	Pre-dose	within 4 hr[b]	START of infusion	X	X	X	X	X		
		End of infusion	within 15 min	END of infusion	X						
		2 hr	±15 min		X						
		4 hr	±15 min		X						
	Day 3	48 hr	+24 hr	START of infusion	X[c]						
	Day 8	Predose	within 4 hr	START of infusion	X						
		End of infusion	Within 15 min	END of infusion	X						
	Day 15	Predose	Within 4 hr	START of infusion	X		X[d]	X[d]	X[d]		
		End of infusion	within 15 min	END of infusion	X						
2	Day 1	Pre-dose	within 4 hr	START of infusion	X	X	X	X	X		
		End of infusion	within 15 min	END of infusion	X						
	Day 15	Pre-dose	within 4 hr	START of infusion			X	X	X		
3, 5, and every 5th cycle thereafter	Day 1	Pre-dose	within 4 hr	START of infusion	X	X	X[e]	X[e]	X[e]		
		End of infusion	within 15 min	END of infusion	X						
6	Day 1	Pre-dose	within 4 hr	START of infusion			X	X	X		
EOT					X	X	X	X			
Additional biopsy											X[a]

a See Section 7.1.2 for details.
b Cycle 1, Day 1 pre-dose window is 24 hours.

c Blood draws at indicated time points may be obtained by a visiting nurse service.
d Draw only for Cycle 1 and Cycle 2.
e Cycle 3 and Cycle 5 only.

Table 19: Pharmacokinetic, immunogenicity, and biomarker sample collection time points – 21 day cycles (Part C; 2q3wk, q1wk)

Cycle	Study Day	Time	Window	Relative Time	LV PK	Pembrolizumab PK	LV ATA	Pembrolizumab ATA	Serum	Plasma	Blood Cell Pellet	Archived tumor specimen	Tumor biopsy (FFPE)
Screening	–28 to 1	N/A	N/A	N/A								X[a]	
1 and 4	Day 1	Pre-dose of LV	within 4 hr[b]	START of LV infusion	X	X	X	X	X	X	X		
		End of LV infusion	within 15 min	END of LV infusion	X								
		End of Pembrolizumab infusion	Within 15 min	End of Pembrolizumab infusion		X[c]							
		2 hr	±15 min	END of LV infusion	X								
		4 hr	±15 min	END of LV infusion	X								
	Day 3	48 hr	+24 hr	START of LV infusion	X[c d]								
	Day 8	Predose of LV	within 4 hr	START of LV infusion	X								
		End of LV infusion	Within 15 min	END of LV infusion	X								
	Day 15	Predose of LV	Within 4 hr	START of LV infusion	X[e]				X[f]	X[f]	X[f]		
		End of LV infusion	within 15 min	END of LV infusion	X[e]								
2	Day 1	Pre-dose of LV	within 4 hr	START of LV infusion	X	X	X	X	X	X	X		
		End of LV infusion	within 15 min	END of LV infusion	X								

Cycle	Study Day	Time	Window	Relative Time	LV PK	Pembrolizumab PK	LV ATA	Pembrolizumab ATA	Serum	Plasma	Blood Cell Pellet	Archived tumor specimen	Tumor biopsy (FFPE)
	Day 15	Pre-dose of LV	within 4 hr	START of LV infusion					X[f]	X[f]	X[f]		
3, 5, and every 5th cycle thereafter	Day 1	Pre-dose of LV	within 4 hr	START of LV infusion	X	X	X	X	X[g]	X[g]	X[g]		
		End of LV infusion	within 15 min	END of LV infusion	X								
6	Day 1	Pre-dose of LV	within 4 hr	START of LV infusion					X	X	X		
EOT					X	X	X	X	X	X			
Additional biopsy													X[a]

[a] See Section 7.1.2 for details.
[b] Cycle 1, Day 1 pre-dose window is 24 hours.
[c] Cycle 1 only
[d] Blood draws at indicated time points may be obtained by a visiting nurse service.
[e] Arm 3 only
[f] Draw only for Cycle 1 and Cycle 2 for Arm 3 only
[g] Cycle 3 and Cycle 5 only

7.4. Biomarker Studies

Samples for exploratory biomarkers will be collected at protocol -specified time points per the schedules provided in Table 17, Table 18, and Table 19. Biomarker assessments will not be used for subject selection. Correlative studies will be conducted to gain a better understanding of target-response relationship, predictive biomarkers, mechanisms of action, resistance mechanisms, and pharmacodynamics. Methods of analysis may include IHC, next generation sequencing, polymerase chain reaction (PCR), multiplex immunofluorescence, flow cytometry, immunoassays, and proteomic methodologies such as enzyme-linked immunosorbent assay (ELISA) and microvesicle assessment.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are too few samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early, completion of biomarker assessments is based on justification and intended utility of the data.

7.4.1. Biomarkers in Blood

The primary effects of LV on tumor cells may lead to changes in the activation state of local, tumor-associated, and peripheral immune cells. Biomarker assessments in blood samples may include measurement of baseline and drug-induced changes in circulating proteins, blood cell populations, immunoassays, gene expression, cytogenetics, genetic polymorphisms, somatic mutations associated with cancer, and circulating immune function and disease markers. LV interactions with peripheral blood cells and tissues may also be monitored. These may provide insight into treatment-related changes in activation state of peripheral immune system associated with LV-induced tumor cell death.

7.4.2. Biomarkers in Tumor Tissue

To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tissue from biopsies taken prior to enrollment will be examined. Biopsies will be assessed for specific pharmacodynamic, predictive, and prognostic biomarkers in the tumor to compare the effects of treatment with LV. If tissue is available from a standard of care biopsy collected after enrollment (until disease progression after treatment with LV), it may also be examined.

7.5. Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue may be retained by Seagen Inc. 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 may be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.6. 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, vital signs, pregnancy testing, and laboratory tests. Safety assessments will be performed at prespecified time points through the EOT visit and in some circumstances beyond the EOT visit. AEs and SAEs will be reported through the EOT visit or 30 days after the last study treatment, whichever is later (see Section 7.6.1.3). For Part C Arm 2 and Arm 3, AEs and SAEs will be reported through the EOT visit or 90 days after the last study treatment, whichever is later (see Section 7.6.1.3).

An ongoing, real-time review of subject safety and SAEs will be conducted by the sponsor's Drug Safety Department.

7.6.1. Adverse Events

7.6.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject 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:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- 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 (during and post-dose) through the end of the safety reporting period (see Section 7.6.1.3). Complications that occur in association with any procedure (eg, 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 (eg, 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 subject 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 subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject 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 subject 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 7.6.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 5. 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 monotherapy or LV plus pembrolizumab combination therapy) 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 (eg, 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 (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, 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

7.6.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject 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 LV. For IRRs, do not use the NCI CTCAE terms of "cytokine release syndrome," "acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom 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 subject (or partner of a male subject) during the trial. If a subject becomes pregnant while on study, the site will contact the subject at least monthly and document the subject'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 subject 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 6 months after the final dose of study drug, or 30 days following the last dose of study drug if the subject initiates new anticancer therapy, whichever is earlier. Include any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 24 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 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 7.6.1.1) 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 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 drug-induced liver injury (DILI).

Definition

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

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

   AND

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

   AND

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 >3 x 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.

The guidance documents below are included in the study binder.

- FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009.
- Health Canada Guidance Document; Pre-market Evaluation of Hepatotoxicity in Health Products, 2012.

7.6.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

For LV monotherapy (Part A, Part B, Part C Arm 1), the safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. For pembrolizumab and LV combination therapy (Part C Arms 2 and 3), the reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 90 days after the last study treatment, whichever is later. 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.

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 subject 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. In particular, these include AEs of peripheral neuropathy in all subjects.

7.6.1.4. 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:

- Subject 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.

7.6.1.5. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.6.1.4).

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 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 to the FDA are progression of the underlying cancer. These anticipated SAEs will be reviewed periodically by the 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.

7.6.1.6. 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 within 24 hours of awareness.

ECIs for this trial include:

1. An overdose of either study product, as defined in Section 5.5.2, and is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is ≥3 x ULN, and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that is <2 x 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). It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the medical monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

7.6.2. Vital Signs

Vital sign measurements are to include heart rate, systolic and diastolic blood pressure, and temperature. All vital signs should be measured after the subject has been sitting/resting.

Part A: Vital signs will be measured on Day 1 of each cycle and recorded within 60 minutes prior to the start of LV infusion and within 30 minutes after completion of LV infusion.

Part B: Vital signs will be measured on Day 1, Day 8, and Day 15 of each cycle and recorded within 60 minutes prior to the start of LV infusion and within 30 minutes after completion of LV infusion.

Part C: Vital signs will be measured on Day 1 and Day 8 of each cycle in Arm 1 and Arm 2, or on Day 1, Day 8, and Day 15 of each cycle in Arm 3. Vital signs will be recorded within 60 minutes prior to the start of LV infusion, within 30 minutes after completion of LV infusion, and during infusion as clinically indicated (Arm 1). 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 (Arm 2 and Arm 3).

7.6.3. Clinical Laboratory Tests

The following safety laboratory assessments will be performed by local laboratories at the designated time points (see Appendix A, Appendix B, Appendix C, and Appendix D) during the course of the study. Results of all clinical laboratory tests except pregnancy and PSA tests are to be submitted to iRIS. Instructions for submission to iRIS are located in the iRIS Manual.

- Serum chemistry panel: including sodium, potassium, blood urea nitrogen/blood urea, creatinine, calcium, albumin, and magnesium.
- Liver function tests including total bilirubin, alkaline phosphatase, ALT, and AST
- CBC with differential: white blood count, hemoglobin, hematocrit and platelets; and the differential including, but not limited to, neutrophils, lymphocytes, and monocytes
- PSA test (prostate cancer patients only)
- Testosterone measurement (at Screening, prostate cancer patients only)
- Blood glucose
    - Fasting blood glucose is only required at screening. If fasting blood glucose is elevated, a repeat assessment must be obtained.
- HbA1c: if HbA1c is elevated during screening, HbA1c assessment must be repeated to confirm
- The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL.

  GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- Thyroid function tests, including TSH, T3 or free T3, and free T4 (Part C Arm 2 and Arm 3).

7.6.4. Physical Examination

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

7.6.5. Pregnancy Testing

For subjects 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 Day 1 of each treatment cycle, at the EOT visit, and 24 weeks after EOT. A negative pregnancy result is required before the subject may receive LV on Day 1 of each 21-day cycle. Pregnancy tests may also be repeated as requested per institutional review board (IRB)/independent ethics committee (IEC) or if required by local regulations.

7.7. 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.

Response will be assessed according to RECIST v1.1 (Appendix H) (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will 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 subjects at the site, Seagen Inc. 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
- Subject coding and randomization (if applicable)
- 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 Inc. representative or designee will typically 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 subjects, 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 Inc. or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

Seagen Inc. 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 subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically 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 and the IRB/IEC.

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 during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality 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 Research and Development Quality group of Seagen Inc. 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 electronic data capture 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 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 Inc., whichever is longer. The investigator must contact Seagen Inc. 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 Inc.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Up to approximately 414 subjects may be enrolled in the study, including up to 72 subjects in Part A (q3wk dosing) with each cohort having up to 12 subjects, up to 252 subjects in Part B (q1wk dosing) with each cohort having up to 30 subjects, and approximately 90 subjects in Part C (monotherapy or combination with pembrolizumab) with each arm having 30 subjects.

Additional cohorts may also be added in future protocol amendments for additional indications, alternative dosing schedule, biopsy/biomarker analysis, and LV based combination therapy.

The sample size is not based on power calculations for a formal hypothesis testing but is selected to provide a degree of characterization of commonly occurring AEs in the safety profile and/or a reasonable estimation precision of ORR.

For a sample size of 30 subjects per cohort/arm, assuming confirmed ORR is between 10% and 50%, and confirmed PSA response rate for CRPC is between 10% and 50%, the 2-sided 90% exact confidence interval (CI) are summarized below:

Confirmed ORR*	90% Exact CI (N=30)
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)

*Including confirmed PSA response rate for CRPC cohort

This sample size of 30 subjects per cohort/arm 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=30)
5%	79%
10%	96%

In Part B, the initial 12 subjects enrolled across the tumor cohorts per dose level will be evaluated for safety after the 12th patient completes the first cycle of treatment. The sample size of 12 allows for a reasonable likelihood of observing a given AE in at least 1 subject even when the incidence of the specific AE is low.

The table below shows the probability of observing an AE in at least 1 subject out of 12 subjects for different underlying incidence of AEs.

Underlying AE Incidence	Probability of Observing the AE in 1 or More Subjects Out of 12 Subjects
1%	11%
5%	46%
10%	72%

9.2. Study Endpoint Definitions

9.2.1. Confirmed ORR

Confirmed ORR is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator. Subjects who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders.

9.2.2. Confirmed PSA Response Rate

Confirmed PSA response rate is defined as the proportion of subjects with a reduction from baseline PSA level of at least 50%, measured twice ≥3 weeks apart.

9.2.3. Disease Control Rate

DCR is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator, or meet the SD criteria at least once after start of study treatment at a minimum interval of 5 weeks or 7 weeks for prostate cancer subjects. Subjects who do not have at least 1 post-baseline response assessment will be counted as non-responders.

9.2.4. Duration of Response

DOR is defined as the time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first.

DOR data will be censored as described below:

- Subjects who do not have PD and are still on study at the time of an analysis will be censored at the date of last disease assessment documenting absence of PD.
- Subjects who started a new anticancer treatment prior to documentation of PD will be censored at the date of last disease assessment prior to the start of new treatment.
- Subjects who are removed from the study prior to documentation of PD will be censored at the date of last disease assessment documenting absence of PD.

DOR will only be calculated for subjects who achieve a confirmed CR or PR as measured by RECIST v1.1 for all tumors.

PSA-DOR is defined as the time from the first documentation of PSA response (subsequently confirmed at least 3 weeks apart) to the first documentation of PSA progression or death due to any cause, whichever comes first.

9.2.5. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the start of study treatment to the first documentation of PD by RECIST v1.1 or clinical PD or by PSA progression (prostate cancer cohort) or death due to any cause, whichever comes first. PSA-PFS is defined in Section 9.2.7.

The same censoring rules as outlined in Section 9.2.4 for DOR will be applied to PFS. Subjects lacking an evaluation of tumor response after their first dose of study drug will have their event time censored at Day 1.

9.2.6. Overall Survival

OS is defined as the time from the 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 subject is known to be alive (i.e., date of last contact).

9.2.7. Prostate-Specific Antigen Progression-Free Survival

PSA-PFS is defined as the time from the start of study treatment to first occurrence of PSA progression or death, whichever comes first.

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 (eg, adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any key changes to the methods described in the final SAP will be described 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 per category for categorical variables.

The 2-sided 90% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (eg, ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 90% CI will be calculated based on the complementary log-log transformation (Collett 1994).

9.3.1.1. Randomization and Blinding

This is an open-label study. Blinding will not be performed. Cohorts in Part A and Part B are single-arm. The cohort in Part C has 3 randomized arms.

For Part C, approximately 90 subjects will be randomized to 1 of the 3 arms with 30 subjects per arm: Arm 1 (monotherapy 2q3wk), Arm 2 (2q3wk combination with pembrolizumab), Arm 3 (q1wk combination with pembrolizumab). The randomization ratio will be 2:1:1 until Arm 1 enrolls 30 subjects. This will ensure that Arm 1 reaches the target enrollment sooner. Thus, of the first 60 subjects, 30 subjects will be enrolled in Arm 1, 15 subjects will be enrolled in Arm 2 and 15 subjects will be enrolled in Arm 3. Afterwards, the remaining subjects will be randomized in a 1:1 ratio to either Arm 2 or Arm 3. Randomization will be stratified according to BRAF mutational status (wild-type versus mutated).

9.3.1.2. Adjustments for Covariates

No adjustments for covariates are planned in the analyses.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Missing AE start date and/or end date will be imputed while calculating duration of events and treatment-emergent status. Missing subsequent anticancer treatment start date will be imputed while deriving the time-to-event endpoints as applicable. Censoring rules will be applied for the analysis of time-to-event endpoints. Details will be provided in the SAP.

9.3.1.4. Multicenter Studies

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

9.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned in this study.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, 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 study drug unless otherwise specified.

9.3.1.7. Analysis Sets

The full analysis set (FAS) includes all subjects who received any amount of study drug. All efficacy analyses will be based on the FAS.

The safety analysis set includes all subjects who received any amount of study drug, and thus is equivalent to the FAS. All safety analyses will be based on the safety analysis set.

The efficacy evaluable analysis set includes subjects who received any amount of study drug and had at least one post-baseline disease assessment per RECIST v1.1 or had clinical progression per investigator judgment or discontinued from study.

The PSA evaluable analysis set includes subjects in the prostate cancer cohort who received any amount of study drug and had both baseline and at least one evaluable post-baseline PSA measurements.

9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

The primary analysis will be conducted when all treated subjects in a cohort have been followed for at least 6 months or come off study, whichever comes first. Subsequent data cutoff dates may be defined to allow for more precise estimates of time-to-event endpoints.

Interim analysis for futility will be performed separately for each cohort in Part A and Part B after approximately 12 subjects of a given cohort have been treated and are efficacy evaluable post-baseline.

9.3.2. Subject Disposition

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

9.3.3. Subject Characteristics

Demographics and other baseline characteristics will be summarized by cohort for the FAS. Details will be provided in the SAP.

9.3.4. Treatment Administration

Treatment administration will be summarized by cohort for the safety analysis set. Summary statistics for duration of therapy, number of cycles per subject, and the number and percentage of subjects treated at each cycle will be presented. Details will be provided in the SAP.

9.3.5. Efficacy Analyses

The primary analysis of efficacy endpoints will be based on the FAS. Supplemental analysis of efficacy endpoints may be performed using the efficacy evaluable analysis set. For the prostate cancer cohort, the confirmed PSA response rate and PSA-PFS will be based on the PSA evaluable analysis set.

9.3.5.1. Primary Efficacy Analyses

The primary endpoint of this study for all tumor types is the confirmed ORR per investigator assessment. The ORR is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1. The ORR of each cohort and its exact 2-sided 90% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

For prostate cancer, confirmed PSA response per investigator assessment is another primary endpoint. The confirmed PSA response is defined as a reduction from baseline PSA level of at

least 50%, measured twice ≥3 weeks apart. The confirmed PSA response rate and its exact 2-sided 90% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

9.3.5.2. Secondary Efficacy Analyses

The DCR will be estimated for each cohort and the 90% CIs will be calculated using the Clopper-Pearson method.

The DOR, PFS, and OS for each cohort, PSA-DOR and PSA-PFS for the prostate cancer cohort will be estimated using the Kaplan-Meier methodology, and the medians and associated 90% CIs will be calculated. Kaplan-Meier plots will be provided as appropriate.

9.3.6. Pharmacokinetic and Immunogenicity Analyses

LV (ADC), total antibody, and MMAE concentrations will be summarized with descriptive statistics at each PK sampling time point. Selected PK parameters for LV, total antibody, and MMAE will be estimated by noncompartmental analysis and summarized using descriptive statistics. These data may be combined with PK data from other clinical trials with LV for population PK and exploratory exposure-response analyses.

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

9.3.7. Biomarker Analyses

Relationships of biomarker parameters (eg, 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. Details will be described separately in the SAP or Biomarker Analysis Plan.

9.3.8. Safety Analyses

All safety analyses will be performed by cohort and overall using the safety analysis set.

9.3.8.1. Extent of Exposure

Duration of treatment, number of cycles, total dose, and dose intensity will be summarized. Dose modifications, including dose delay, dose reduction, and unplanned dose adjustment, will be summarized. Details will be provided in the SAP.

9.3.8.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, TEAEs, treatment-related AEs, Grade 3 and higher TEAEs, 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.

TEAEs 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 subject, the AE will be counted once as the occurrence. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.8.3. 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.

9.3.8.4. Clinical Laboratory Results

Summary statistics of laboratory results and changes from baseline will be tabulated by scheduled visit. Grading of laboratory values will be assigned programmatically per the NCI CTCAE v5.0. Shift tables comparing the worst post-baseline to baseline CTCAE grade will be presented. Laboratory values will be listed with grade per CTCAE and flagged when values are outside the normal reference range.

9.3.8.5. Other Safety Analyses

Vital Signs

Vital signs data will be listed. Summary statistics of vital signs and change from baseline may be tabulated where appropriate.

ECOG Status

ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

9.3.9. Interim Analyses

Interim analysis for futility will be performed separately for each cohort in Part A and Part B after approximately 12 subjects of a given cohort have been treated with a specific LV dose and schedule (LV q3wk at 2.5 mg/kg, LV q1wk at 1.0 mg/kg, or LV q1wk at 1.25 mg/kg [Section 3.1]) and are efficacy evaluable post-baseline. Enrollment to each cohort may be held after approximately 12 subjects for interim futility analysis of the respective cohorts.

The Bayesian predictive probability of success (PPoS) approach will be used to determine the futility criteria (Lee 2008). At the time of each interim analysis, the PPoS will be calculated. PPoS is the probability of achieving "success" should the cohort be continued to the maximum sample size of 30 given the data observed at interim, and a cohort is considered "success" if the posterior probability that the ORR exceeds the response rate of current standard of care (i.e., 15% for SCLC, 10% for NSCLC-squamous, 15% for NSCLC-nonsquamous, 10% for HNSCC, 10% for esophageal-squamous, 15% for gastric and GEJ adenocarcinoma, 10% for melanoma, and 30% for CRPC as referenced in Section 3.1) is greater than 90%.

The ORR observed at interim will be counted as a response for the calculation of PPoS. Table 20 summarizes the PPoS based on the number of responses observed among the first 12 subjects.

Table 20: PPoS based on response among the first 12 subjects

No. of responses[a] among the first 12 subjects	Predictive Probability of Success							
	SCLC (p_0=15%)	NSCLC-squamous (p_0=10%)	NSCLC-nonsquamous (p_0=15%)	HNSCC (p_0=10%)	Esophageal-squamous (p_0=10%)	Gastric or GEJ adenocarcinoma (p_0=15%)	Melanoma (p_0=10%)	CRPC (p_0=30%)
0	0.05%	0.2%	0.05%	0.2%	0.2%	0.05%	0.2%	0.0007%
1	2%	8%	2%	8%	8%	2%	8%	0.05%
2	16%	36%	16%	36%	36%	16%	36%	0.8%
3	45%	73%	45%	73%	73%	45%	73%	6%
4	77%	94%	77%	94%	94%	77%	94%	21%
5	94%	100%	94%	100%	100%	94%	100%	48%

p_0 is the response rate of current standard of care of each cohort
a Including both confirmed and unconfirmed CR or PR observed at interim

If the PPoS is <10% (i.e., ≤1 response among the first 12 subjects, or ≤3 responses among the first 12 prostate cancer subjects), the data indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort given interim results and the cohort could be stopped early due to insufficient activity. On the other hand, if the PPoS is >90%, the data suggests that if the same trend continues, there is a high probability to conclude a "success" at the end of the cohort. The PFS and OS will also be evaluated at the time of the interim analysis. Based on the efficacy and safety data, together with the PPoS, a cohort may be stopped early by the sponsor.

The predictive probability method allows the PPoS be computed at any interim time and provides flexibility in monitoring treatment activity continuously after the initial interim analysis.

In addition to the interim analysis for futility, interim data from the study may be presented at scientific meetings such as the annual meetings of the ASCO and the European Society for Medical Oncology.

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 2013), and all applicable regulatory requirements.

10.1. Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects 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 subject, or legally acceptable representative, 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.

For phase 1 studies, it is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

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 (eg, 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 subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects 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 subject medical records in the subject 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 subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject 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 subject 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 FOR SCREENING/BASELINE (PARTS A, B, AND C)

	Assessment	Screening/Baseline	
	Day (D)	D –28 to 1	D –7 to 1
	Visit window		
Screening/ Baseline Assessments	Inclusion/Exclusion, medical history	X	
	Informed consent	X	
	Tumor biopsy	X[a]	
	Pregnancy test (females of childbearing potential only)		X[b]
	HbA1c and fasting blood glucose	X[c]	
	PSA (prostate cancer subjects)	X	
	Testosterone (prostate cancer subjects)	X	
	Brain CT or MRI	X	
Safety Assessments	Physical exam		X[d]
	Weight		X
	CBC with differential		X
	Chemistry panel and liver function tests		X
	Thyroid function test[e]	X	
	eGFR		X
	Vital signs		X
	ECOG performance status		X
	Concomitant medications	Related to study procedures	
	AE collection		
Response Baseline Assessments	CT/MRI[f]	X	
	CT/MRI for prostate cancer subjects[f]	X	
	Bone scan for prostate cancer subjects[f]	X	

[a] Archived sample or fresh biopsy if archived sample is not available, see Section 6; (fine-needle aspiration and bone samples are not suitable).

[b] Pregnancy test must be performed within 3 days prior to C1 Day 1.

[c] If either baseline HbA1c or baseline fasting glucose is elevated, repeat assessments must be obtained, see Section 7.6.3.

[d] Include assessment of height.
e Part C, Arm 2 and 3 only. See Section 7.6.3 .
[f] See Section 7.2.1 for tumor cohort specific imaging requirements. Submit copies of images to sponsor's designee for central review (see Section 6.6).

APPENDIX B. SCHEDULE OF EVENTS FOR TREATMENT (Q3WK DOSING; PART A)

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		± 2d[b]	+ 1d	± 2d	± 2d	± 2d	+ 1d	± 2d	± 2d		± 3d or ± 7d
	Confirm subject meets dosing criteria		X				X					
Treatment	LV administration	Submit eligibility confirmation to sponsor prior to treatment	X				X					
	G-CSF			X[c]				X[c]				
Safety Assessments	Pregnancy test (females of childbearing potential only)		X[d]				X				X	X[e]
	HbA1c										X	
	Physical exam		X[d]		X	X	X				X	X[f]
	Weight		X[d]				X				X	
	CBC with differential		X[d]		X	X	X		X[g]	X[g]	X	
	Chemistry panel and liver function tests		X[d]		X	X	X		X[g]	X[g]	X	
	Random blood glucose		X				X					
	Vital signs[k]		X				X				X	
	ECOG performance status		X[d]				X				X	
	Concomitant medications	Related to study procedures	Collect from Day 1 predose to EOT or 30 days post last dose, whichever is later									
	AE collection											
Biomarker Assessments	Blood samples for biomarker assessment (see Section 7.4.1)		See Table 17									
	Tumor biopsy for research (see Section 7.4.2)											

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		± 2d[b]	+ 1d	± 2d	± 2d	± 2d	+ 1d	± 2d	± 2d		± 3d or ± 7d
PK/ATA	Samples for PK testing (see Section 7.3)		See Table 17									
	Samples for ATA testing (see Section 7.3)											
Response Assessments	CT/MRI[h]		Every 6 weeks (± 3 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter[i]								X[j]	X[f]
	Survival follow-up contact											X[f]

D=day, F/U=follow-up.

a EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

b Visit window does not apply to C1, Day 1.

c For subjects receiving >200 mg LV per infusion (weigh >80 kg at baseline), prophylactic G-CSF administration is required after LV administration (may begin on Days 2, 3, or 4). If pegfilgrastim is used, a one-time dose per cycle is recommended. If daily myeloid growth factor support is used, treat for least 5–7 days or until the ANC is >1000/mm^3 (≤ Grade 2); see Section 5.4.1.

d Not required in Cycle 1 if baseline was assessed within 3 days prior to first dose of study drug.

e Only tested once at 24 weeks after last dose of LV.

f Every 6 weeks (± 3 days) for the first 12 months after the first dose of LV, then every 12 weeks (± 7 days) thereafter. Continue to assess until disease progression. After a year of follow-up, reducing scanning frequency to institutional standard of care

g Required only for Cycle 2.

h See Section 7.2.1 for tumor cohort-specific imaging requirements. Submit copies of images to independent review facility.

i If required, it is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

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

k Vital signs to be within 60 minutes prior to the start of LV infusion and within 30 minutes after completion of LV infusion.

APPENDIX C. SCHEDULE OF EVENTS FOR TREATMENT (Q1WK DOSING; PART B)

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		± 2d[b]	+ 1d	± 2d	± 2d	± 2d	+ 1d	± 2d	± 2d		± 3d or ± 7d
	Confirm subject meets dosing criteria		X		X	X	X		X	X		
	PSA test[c]		X[d]				X				X	X
Treatment	LV administration	Submit eligibility confirmation to sponsor prior to treatment	X		X[k]	X[k]	X[k]		X[k]	X[k]		
Safety Assessments	Pregnancy test (serum or urine; females of childbearing potential only)		X[d]				X				X	X[e]
	HbA1c										X	
	Physical exam		X[d]		X	X	X				X	X[f]
	Weight		X[d]				X				X	
	CBC with differential		X[d]		X[m]	X[m]	X		X[m]	X[m]	X	
	Serum chemistry panel and liver function tests		X[d]		X[m]	X[m]	X		X[m]	X[m]	X	
	Random blood glucose[j]		X		X[j]	X[j]	X		X[j]	X[j]		
	Vital signs[l]		X		X	X	X		X	X	X	
	ECOG performance status		X[d]				X				X	
	Concomitant medications	Related to study procedures	Collect from Day 1 predose to EOT or 30 days post last dose, whichever is later									
	AE collection											
Biomarker Assessments	Blood samples for biomarker assessment (see Section 7.4.1)		See Table 18									

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		± 2d[b]	+ 1d	± 2d	± 2d	± 2d	+ 1d	± 2d	± 2d		± 3d or ± 7d
	Tumor biopsy for research (see Section 7.4.2)											
PK/ATA	Samples for PK testing (see Section 7.3)		See Table 18									
	Samples for ATA testing (see Section 7.3)											
Response Assessments	CT/MRI for non-prostate cancer subjects[g]		Every 6 weeks (±3 days) for the first 12 months, then every 12 weeks (±7 days) thereafter[h]								X[i]	X[f]
	CT/MRI for prostate cancer subjects[g]		Every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter[h]								X[i]	X[f]
	Bone scan (prostate cancer subjects only)[g]		Every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter[h]								X[i]	X[f]
	Survival follow-up contact											X[f]

D=day, F/U=follow-up.

a EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

b Visit window does not apply to Cycle 1, Day 1.

c PSA test on Day 1 of each cycle or, once every 3 weeks (±3 days) per calendar. For F/U, PSA test every 12 weeks (±7 days).

d Not required in Cycle 1 if baseline was assessed within 3 days prior to first dose of study drug.

e Only tested once at 24 weeks after last dose of LV.

f Every 6 weeks (± 3 days) for the first 12 months after the first dose of LV, then every 12 weeks (± 7 days) thereafter. Continue to assess until disease progression. After a year of follow-up, reduce scanning frequency to institution's standard of care. For F/U in prostate cancer subjects, CT/MRI and bone scans every 12 weeks (±7 days)

g See Section 7.2.1 for tumor cohort-specific imaging requirements. Submit copies of images to independent review facility.

h If required, it is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

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

j Random blood glucose should be checked prior to dosing on Day 1 of each 21-day cycle; and on Day 8 and Day 15 of Cycle 1 and 2. Following Cycle 2, it may be checked on days 8 and 15 as indicated, particularly in subjects at risk for hyperglycemia (Section 5.6).

k A +2 day dosing window is allowed. At least 7 days must elapse between administrations of LV.

l Vital signs to be within 60 minutes prior to the start of LV infusion and within 30 minutes after completion of LV infusion

m Only required for Cycle 1 and Cycle 2.

APPENDIX D. SCHEDULE OF EVENTS FOR TREATMENT (PART C)

Arms 1 and 2 (2q3wk dosing)

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		0d[b]	+ 1d	+ 4d	– 2d	+ 4d	+ 1d	+ 4d	– 2d		± 3d or ± 7d
	Confirm subject meets dosing criteria		X		X		X		X			
Treatment	LV administration	Submit eligibility confirmation to sponsor prior to treatment	X		X[c]		X[c]		X[c]			
	Pembrolizumab administration (Arm 2)		X				X					
Safety Assessments	Pregnancy test (females of childbearing potential only)		X[d]				X				X	X[e]
	HbA1c										X	
	Physical exam		X[d]		X	X	X				X	X[f]
	Weight		X[d]				X				X	
	CBC with differential		X[d]		X[g]	X[g]	X		X[g]	X[g]	X	
	Chemistry panel and liver function tests		X[d]		X[g]		X		X[g]		X	
	Random blood glucose[h]		X		X		X					
	Thyroid function tests (Arm 2)[i]		On Day 1 of each odd-numbered cycle while on treatment (eg, Cycles 1, 3, 5, etc)									
	Vital signs[j]		X		X		X		X		X	
	ECOG performance status		X[d]				X				X	

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		0d[b]	+ 1d	+ 4d	– 2d	+ 4d	+ 1d	+ 4d	– 2d		± 3d or ± 7d
	Concomitant medications	Related to study procedures	**Arm 1**: Collect from Day 1 predose to EOT or 30 days post last dose, whichever is later **Arm 2:** Collect from Day 1 predose to EOT or 90 days post last dose, whichever is later									
	AE collection	Related to study procedures										
Biomarker Assessments	Blood samples for biomarker assessment (see Section 7.4.1)		See Table 19									
	Tumor biopsy for research (see Section 7.4.2)											
PK/ATA	Samples for PK testing (see Section 7.3)		See Table 19									
	Samples for ATA testing (see Section 7.3)											
Response Assessments	CT/MRI[k]		Every 6 weeks (± 3 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter[l]								X[m]	X[f]
	Survival follow-up contact											X[f]

2q3wk=dosing on Day 1 and Day 8 but not Day 15 of each 21-day cycle; D=day; F/U=follow-up

[a] EOT evaluations should be obtained before the initiation of non protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

[b] Visit window does not apply to C1, Day 1.

[c] A +4 day dosing window is allowed. At least 7 days must elapse between administrations of LV.

[d] Not required in Cycle 1 if baseline was assessed within 3 days prior to first dose of study drug.

[e] Only tested once at 24 weeks after last dose of LV

[f] Every 6 weeks (± 3 days) for the first 12 months after the first dose of LV, then every 12 weeks (± 7 days) thereafter. Continue to assess until disease progression. After a year of follow up, reducing scanning frequency to institutional standard of care

[g] Only required for Cycle 1 and Cycle 2.

[h] Random blood glucose should be checked prior to dosing on each dosing day of the first 2 cycles. For Cycle 3 and later, blood glucose should be checked on Day 1 of each cycle and may be checked on Day 8 if clinically indicated, particularly in subjects at risk for hyperglycemia (Section 5.6).

[i] Thyroid function tests include TSH, T3 or free T3, and free T4

[j] Arm 1: Vital signs to be within 60 minutes prior to the start of LV infusion, within 30 minutes after completion of LV infusion, and during infusion as clinically indicated.
Arm 2: Vital signs to be within 60 minutes prior to the start of 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.

[k] See Section 7.2.1 for tumor cohort specific imaging requirements. Submit copies of images to independent review facility.

[l] If required, it is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

[m] Not required if conducted within 4 weeks prior to EOT.

Arm 3 (q1wk dosing)

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		+ 2d[b]	+ 1d	+ 2d	+ 2d	+ 2d	+ 1d	+ 2d	+ 2d		± 3d or ± 7d
	Confirm subject meets dosing criteria		X		X	X	X		X	X		
Treatment	LV administration	Submit eligibility confirmation to sponsor prior to treatment	X		X[c]	X[c]	X[c]		X[c]	X[c]		
	Pembrolizumab administration		X				X					
Safety Assessments	Pregnancy test (females of childbearing potential only)		X[d]				X				X	X[e]
	HbA1c										X	
	Physical exam		X[d]		X	X	X				X	X[f]
	Weight		X[d]				X				X	
	CBC with differential		X[d]		X[g]	X[g]	X		X[g]	X[g]	X	
	Chemistry panel and liver function tests		X[d]		X[g]	X[g]	X		X[g]	X[g]	X	
	Random blood glucose[h]		X		X	X	X		X	X		
	Thyroid function tests[i]		On Day 1 of each odd-numbered cycle while on treatment (eg, Cycles 1, 3, 5, etc)									
	Vital signs[j]		X		X	X	X		X	X	X	
	ECOG performance status		X[d]				X				X	
	Concomitant medications	Related to study procedures	Collect from Day 1 predose to EOT or 90 days post last dose, whichever is later									
	AE collection											
Biomarker Assessments	Blood samples for biomarker assessment (see Section 7.4.1)		See Table 19									

	Assessment	Enrollment	Cycle 1				Cycle 2+				EOT	F/U
	Day	Within 7D of 1st dose	D1	D3	D8	D15	D1	D3	D8	D15	Within 30–37D of last dose[a]	Every 6 or 12 weeks
	Visit window		+ 2d[b]	+ 1d	+ 2d	+ 2d	+ 2d	+ 1d	+ 2d	+ 2d		± 3d or ± 7d
	Tumor biopsy for research (see Section 7.4.2)											
PK/ATA	Samples for PK testing (see Section 7.3)		See Table 19									
	Samples for ATA testing (see Section 7.3)											
Response Assessments	CT/MRI[k]		Every 6 weeks (± 3 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter[l]								X[m]	X[f]
	Survival follow-up contact											X[f]

D=day; F/U=follow-up; q1wk=dosing on Day 1, Day 8, and Day 15 of each 21-day cycle

[a] EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

[b] Visit window does not apply to C1, Day 1.

[c] A +2 day dosing window is allowed. At least 7 days must elapse between administrations of LV.

[d] Not required in Cycle 1 if baseline was assessed within 3 days prior to first dose of study drug.

[e] Only tested once at 24 weeks after last dose of LV.

[f] Every 6 weeks (± 3 days) for the first 12 months after the first dose of LV, then every 12 weeks (± 7 days) thereafter. Continue to assess until disease progression. After a year of follow up, reducing scanning frequency to institutional standard of care

[g] Only required for Cycle 1 and Cycle 2.

[h] Random blood glucose should be checked prior to dosing on each dosing day of the first 2 cycles. For Cycle 3 and later, blood glucose should be checked on Day 1 of each cycle and may be checked on Day 8 and/or Day 15 if clinically indicated, particularly in subjects at risk for hyperglycemia (Section 5.6)

[i] Thyroid function tests include TSH, T3 or free T3, and free T4

[j] Vital signs to be within 60 minutes prior to the start of 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.

[k] See Section 7.2.1 for tumor cohort specific imaging requirements. Submit copies of images to independent review facility.

[l] If required, it is recommended that scans not be scheduled on the dosing day. It is recommended that scans done on the same day as Day 1 of subsequent cycles be completed and reviewed prior to infusion with LV.

[m] Not required if conducted within 4 weeks prior to EOT.

APPENDIX E. NEW YORK HEART ASSOCIATION CLASSIFICATION

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

APPENDIX F. P-GP AND CYP3A INDUCERS/INHIBITORS

Subjects who are receiving P-gp or CYP3A4 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 Inc., March 2018), 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.

Additional new drugs and marketed drugs may be identified as inducers/inhibitors with continued research.

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
ranolazine	indinavir and ritonavir
ritonavir	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/ritonavir*

* P-gp inducer only

Note: Any additional P-gp inducers/inhibitors or strong CYP3A inducers/inhibitors that are identified or become commercially available while the clinical trial is ongoing should also be closely monitored for adverse reactions.

APPENDIX G. PROPHYLACTIC GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) THROUGHOUT SUPPORT RECOMMENDATIONS

In Part A: Starting with the first cycle of LV and continuing through subsequent cycles, prophylactic G-CSF is recommended for subjects who have approximately 20% or higher risk of febrile neutropenia. Subjects who receive >200 mg of LV per infusion (weight >80 kg for dose level 2.5 mg/kg) must be given prophylactic G-CSF, starting with their first dose of >200 mg. It is also strongly recommended that these subjects continue to receive prophylactic G-CSF at subsequent cycles regardless of the LV dose. Therefore, subjects to receive >200 mg LV per infusion must not have contraindications to G-CSF and must be willing to receive them.

Strongly consider primary prophylaxis when allowed per protocol based on subject, 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

In Part A: Secondary prophylaxis with G-CSF is required for all subsequent cycles for subjects who experience Grade 4 neutropenia or febrile neutropenia of any grade in any cycle while on LV (for which primary prophylaxis was not received), must receive G-CSF in all subsequent cycles. **G-CSF support is also required for treatment of febrile neutropenia.**

In Part B and Part C: Secondary prophylaxis with G-CSF is recommended for all subsequent cycles for subjects who experience a neutropenic complication with a previous cycle of therapy (for which primary prophylaxis was not received) when dose reduction or delay may compromise treatment outcome with LV. In Part B and Part C, primary prophylactic G-CSF is not required but is allowed.

In Part B and Part C: Treatment with G-CSF is strongly recommended for subjects 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 109/L)
- Neutropenia expected to last >7 days
- Uncontrolled primary disease
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at time of fever
- Prior episode of febrile neutropenia

As per ASCO guidelines, prophylactic G-CSF should start 1–3 days after LV administration. G-CSF (including pegfilgrastim) should not be given within 24 hours prior to the dose of LV. If pegfilgrastim is used, a one-time dose per cycle is recommended. If daily G-CSF is used, treat for least 5–7 days or until the ANC is >1000/mm^3 (≤ Grade 2). Refer to the Prescribing

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

Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

Guideline Question

How should colony-stimulating factors (CSFs) be used in people with cancer?

Target Population

Adults or children with a solid tumor or lymphoma treated with chemotherapy

Target Audience

Medical oncologists, hematologists, oncology nurses, other clinicians who care for people with cancer, and patients

Methods

An Update Committee was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Key Points

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Secondary prophylaxis with a CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Dose-dense regimens with CSF support should only be used if supported by convincing efficacy data or within an appropriately designed clinical trial. Efficacy data support the use of dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and the use of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin lymphoma, and it cannot routinely be recommended at this time. (Type: evidence based, benefits outweigh harms. Evidence quality: high for breast cancer and lymphoma; intermediate for urothelial cancer. Strength of recommendation: strong for breast cancer and lymphoma; moderate for urothelial cancer.)
- CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: evidence based, benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.)

- CSFs should be administered after autologous stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs may be administered after allogeneic stem-cell transplantation to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak).
- Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥65 years treated with curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) should be considered, particularly in the presence of comorbidities. (Type: evidence based, benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)
- The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable as primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- CSFs should not be used in pediatric patients with nonrelapsed acute lymphoblastic leukemia or nonrelapsed acute myeloid leukemia who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)
- Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and clinical situation. There have been no additional data comparing granulocyte CSFs and granulocyte-macrophage CSFs since the 2006 update; therefore, there is no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)
- Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death resulting from injury to other organs, include the prompt administration of CSFs or pegylated granulocyte CSFs. (Type: formal consensus [by others], benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

Qualifying Statements

The Update Committee did not provide recommendations regarding the use of CSFs in adult patients with acute myeloid leukemia or myelodysplastic syndromes.

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/wbcgf. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Reference: (Smith 2015)

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 H. RECIST 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 v1.1 (Eisenhauer 2009)

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

Response will also be assessed using iRECIST guidelines for determining eligibility of treatment continuation (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.

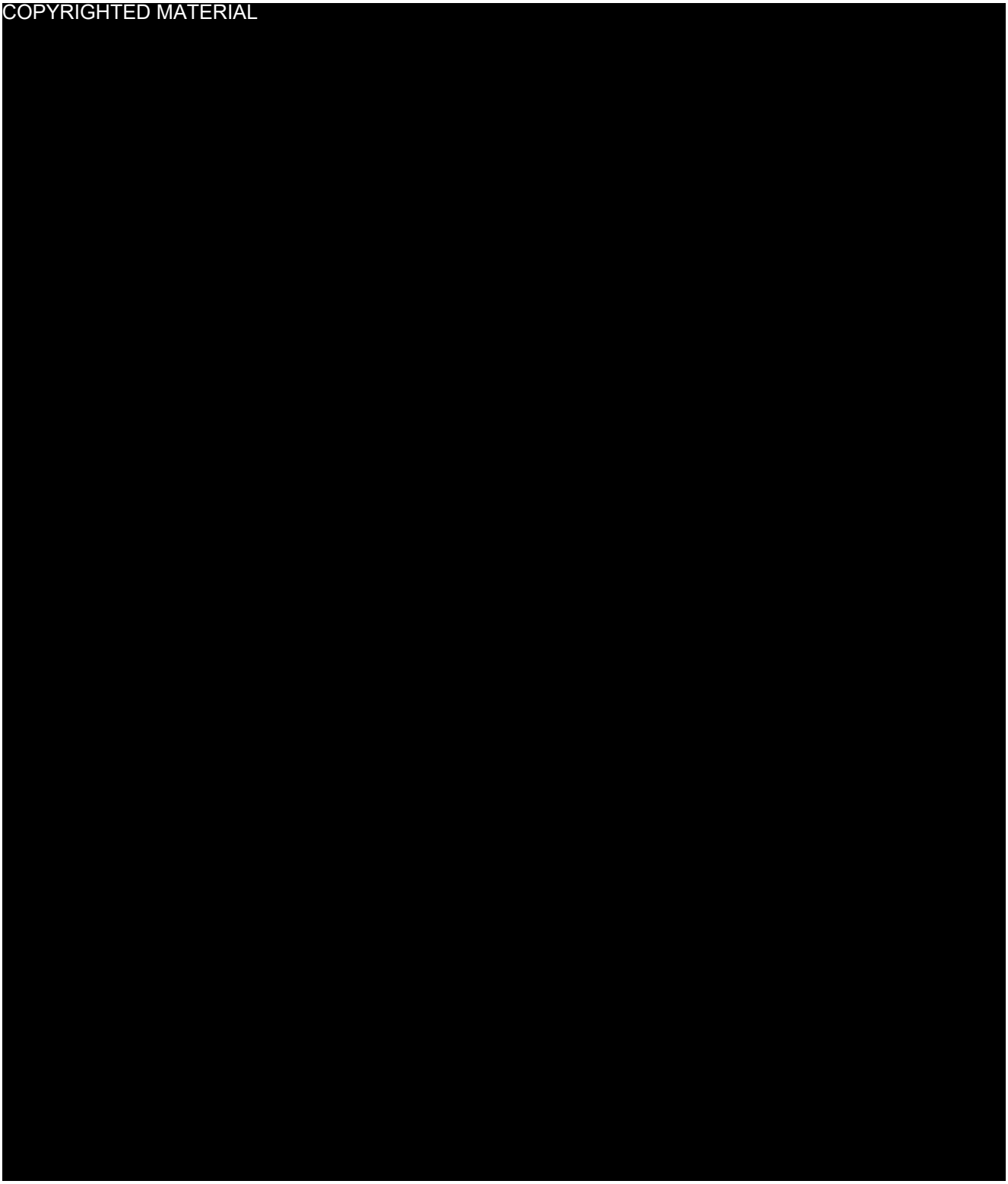
If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD (stable disease), iPR (partial response), or iCR (confirmed response) if those criteria are met compared to baseline).

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.

APPENDIX J. PERFORMANCE STATUS SCALES CONVERSION



APPENDIX K. 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 systemic exposure (at least 6 months after the final dose of study drug; see Section 4.1).

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:
• Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
• 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 (eg, 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 L. PCWG3 SUGGESTED OUTCOME MEASURES FOR CLINICAL TRIALS IN METASTATIC PROSTATE CANCER

Variable	PCWG3 (2015)
Blood-based markers (PSA)	• Recognize that a favorable effect on PSA may be delayed for ≥12 weeks, even for a cytotoxic drug • Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression • Ignore early rises (before 12 weeks) in determining PSA response • For control/relieve/eliminate endpoints: Record the percent change from baseline (rise or fall) at 8–9 or 12 weeks, depending on trial design, and separately, the maximal change (rise or fall) at any time using a waterfall plot • Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL; primary radiation therapy-treated patients who achieved a nadir less than 0.5 ng/mL • Describe absolute changes in PSA over time from baseline to best response • For delay/prevent end points (progression): After decline from baseline: record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later (i.e., a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%. • Recording the duration of PSA decline of little value • No decline from baseline: PSA progression ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks • Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present
Imaging biomarkers: nodal and visceral For control/relieve/eliminate endpoints: General	• Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately • Record up to five lesions per site of disease • Use RECIST v1.1 with caveats: • Record changes in size using waterfall plot • Confirm favorable change with second scan • Record complete elimination of disease at any site separately
Nodes	• Only report changes in lymph nodes that were ≥1.5 cm in the short axis • Record changes in pelvic (regional) nodes; extrapelvic (distant/metastatic) nodes separately

Visceral	• Use RECIST v1.1 with caveats: • Record changes in liver, lung, adrenal, and CNS separately • Only report changes in lesions ≥1.0 cm in the longest dimension
<u>For delay/prevent endpoints:</u> Nodal and visceral	<u>General:</u> • Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately • Use RECIST v1.1 but clearly record type of progression (growth of existing lesions; development of new lesions) separately by site • The recommendations apply to both nmCRPC and mCRPC • Record up to 5 lesions per site of spread • Report the proportion who have not progressed at fixed time points (6 or 12 months) • Note that for some treatments, a lesion may increase in size before it decreases
Nodal	• Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed • Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable • For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST v1.1
Imaging biomarkers: bone Metastatic	<u>For control/relieve/eliminate end points:</u> • Record changes as improved or stable (no lesions), worse (new lesions), or resolved bone lesions • Changes in intensity of uptake alone do not constitute progression or regression • No new lesions: continue therapy in absence of other signs of progression • New lesions (see Progression below) <u>For delay/prevent end points (progression):</u> Progression: • Exclude pseudo progression in the absence of symptoms or other signs of progression • If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 lesions were documented • For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan • Date of progression is the date of the scan that first documents the second lesion

	• Changes in intensity of uptake alone do not constitute either progression or regression • Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)

mCRPC=metastatic castration-resistant prostate cancer; nmCRPC=nonmetastatic castration-resistant prostate cancer; PCWG3=Prostate Cancer Clinical Trials Working Group 3
Reference: (Scher 2016)

APPENDIX M. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors

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 N. DOCUMENT HISTORY

Version	Date
Original	22-April-2019
Amendment 01	23-March-2020
Amendment 02	27-August-2020
Amendment 03	12-October-2020
Amendment 04	02-November-2022

SUMMARY OF CHANGES IN AMENDMENT 01

Section(s)	Change	Rationale
Synopsis, 3.1, 3.2.2, 3.2.3, 3.2.4, 4.1, 4.2, 5.1, 5.2.3, 5.2.4.1, 5.2.4.2, 5.3.1, 5.3.3, 5.5, 6.2, 6.3, 6.6, 7.3, 7.4, 7.6.2, 9.3.1.9, 9.3.9, Appendix B, Appendix C	Added a weekly LV dosing schedule for all cohorts (tumor types) (Part B [q1wk dosing]). The existing dosing schedule for LV every 3 weeks is defined as Part A (q3wk dosing). Wording throughout the protocol was revised to reflect Part A and Part B as appropriate. Affected sections include: • Study design • Rationale for study design • Study population • Treatment administered • Dose and administration • Dose modifications • Concomitant therapy • Management of hyperglycemia • Schedule of events for Part B • Determination of sample size • Safety assessments • Timing of analyses • Interim analyses • PK, ATA, and biomarker sampling time points for Part B	To evaluate weekly LV dosing
Synopsis, 9.1	Sample size was revised to reflect the revised design with the addition of subjects to be enrolled in Part B (LV q1wk dosing) and a smaller number of subjects to be included in Part A (LV q3wk dosing) (revisions shown below for Section 9.1): Up to approximately ~~180~~ **264** subjects may be enrolled in the **entire** study**, including up to 72 subjects in Part A (LV 2.5 mg/kg every 3 weeks [q3wk] dosing) and up to 192 subjects in Part B (LV every 1 week [q1wk] dosing).**~~with up to 30 subjects enrolled in each cohort. In addition, the cohorts may be expanded to enroll additional subjects to better characterize LV activity. A cohort may be expanded to further characterize antitumor activity if the safety profile is acceptable, other efficacy endpoints are comparable to current standard of care, and the confirmed ORR meets cohort specific criteria. Additional cohorts may also be added in future protocol amendments for additional indications, alternative dosing schedule, biopsy/biomarker analysis, and LV-based combination therapy.~~	
Synopsis, 3.1	Corrected timing of repeat scans for confirmed objective responses: Objective responses will be confirmed with repeat scans ~~4~~**6** ~~6~~**4–6** weeks after the first documentation of response.	Correction

Section(s)	Change	Rationale
4.1	Subjects ~~with known deficient mismatch repair (dMMR) and/or microsatellite instability-high (MSI-H)~~ may have received prior anti-PD(L)1 therapy, unless contraindicated.	To allow for any subject in Cohort 6 who meets criteria for receiving anti-PD(L)1
4.2	Other serious **or uncontrolled** underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up (eg, active cardiac disease, active systemic infection, **chronic conditions,** any psychiatric or substance abuse disorders), interfere with the subject's cooperation with the requirements of the trial, place the subject at undue risk of SAE, or make the subject unable to receive sustained therapy	To provide clarification
5.2.3	LV ~~at a dose of 2.5 mg/kg (maximum dose of 250 mg per cycle) will be~~ **is** administered ~~on Day 1 of every 21-day cycle~~ by IV infusion given over approximately 30 minutes. LV must not be administered as an IV push or bolus. **In the absence of infusion-related reactions, 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).**	To provide clarification regarding the infusion rate
5.2.3.1	Added section "Dosing Criteria"	To provide laboratory criteria that must be met prior to dosing on Day 1 of each cycle
5.2.4.2 (Table 5-2)	Changed "Elevated blood glucose" to "Hyperglycemia" in Table 5-2.	To provide clarification
5.3.3	Added section "Myeloid Growth Factors"	To provide further detail regarding use of myeloid growth factors
5.5	Deleted language indicating that finger stick tests for random blood glucose assessment are excluded and added that blood glucose may be measured by blood glucose meter or laboratory-performed blood glucose test.	To obtain results in a timely manner prior to dosing.
	Added the following: **Note: For AE reporting purposes, the severity of hyperglycemia in the NCI CTCAE, version 5, is graded by the medical management required to address hyperglycemia and not by the value of glucose measurement.**	To provide clarification
6.2.1, 7.1, Appendix A	Added brain CT or MRI scan to screening/baseline assessments for Part A.	To assess for brain metastases, consistent with exclusion criterion #3

Section(s)	Change	Rationale
6.6	All subjects will be followed for survival until death or study closure, whichever occurs first. ~~The first follow-up visit will occur 12 weeks (± 7 days) from the most recent prior radiographic response evaluation. Subsequent follow-up visits will be scheduled for 12 weeks (± 7 days) from the previous follow-up visit.~~ Survival and subsequent anticancer therapy follow-up may be conducted with clinic visits or telephone calls.	To provide correction and reflect current study practice
6.6, Appendix B	Revised timing of CT/MRI scans from every 12 weeks to every 6 weeks for subjects who discontinue study treatment for reasons other than disease progression.	Clarification for consistency across sections
7.2	Revised language regarding guidance on use of CT or MRI. For subjects unable to tolerate contrast-enhanced CT assessments, MRI imaging is acceptable. MRI scans **may** ~~are~~ not **be** appropriate **to assess lung parenchymal lesions and CT without contrast enhancement is acceptable in such situations** ~~for NSCLC subjects~~.	To reflect a previous response to health authorities
7.2	Added reference to study imaging manual.	To provide reference for further details regarding CT and MRI assessments
7.3	References to the IRIS Manual were changed to the Laboratory Manual for processing of samples for PK and immunogenicity assessments.	To reflect current study practice
7.6	Added clarifying language regarding timing of 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, vital signs, pregnancy testing, and laboratory tests. Safety assessments will be performed at prespecified time points through the EOT visit **and in some circumstances beyond the EOT visit**. **AEs and SAEs will be reported through the EOT visit or 30 days after the last study treatment, whichever is later (see Section 7.6.1.3)**.	Clarification
7.6.3	Description of the CBC test was clarified to indicate that the standard differential includes, but is not limited to, neutrophils, lymphocytes, and monocytes.	Clarification
9.1	Added language and table to describe rationale for 12-subject safety run-in for Part B. **In Part B, the initial 12 subjects enrolled across the tumor cohorts per dose level will be evaluated for safety after the 12th patient completes the first cycle of treatment. The sample size of 12 allows for a reasonable likelihood of observing a given AE in at least 1 subject even when the incidence of the specific AE is low.**	To provide rationale for design of Part B.

<table>
<tr><th>Section(s)</th><th>Change</th><th>Rationale</th></tr>
<tr><td></td><td>The table below shows the probability of observing an AE in at least 1 subject out of 12 subjects for different underlying incidence of AEs.
<table><tr><th>Underlying AE Incidence</th><th>Probability of Observing the AE in 1 or More Subjects Out of 12 Subjects</th></tr><tr><td>1%</td><td>11%</td></tr><tr><td>5%</td><td>46%</td></tr><tr><td>10%</td><td>72%</td></tr></table></td><td></td></tr>
<tr><td>Appendix I</td><td>Updated guidance on contraception.</td><td>To comply with Clinical Trial Facilitation Group (CTFG) guidelines</td></tr>
<tr><td>Multiple sections</td><td>Minor editorial corrections and clarifications made in some sections of the protocol.</td><td>Corrections and clarifications</td></tr>
</table>

SUMMARY OF CHANGES IN AMENDMENT 02

Section(s)	Change	Rationale
Page 1	Added EudraCT Number to Title page	Added per protocol template requirement
List of Abbreviations	Added castration-resistant prostate cancer (CRPC), computed tomography/magnetic resonance imaging (CT/MRI), Prostate Cancer Clinical Trials Working Group 3 (PCWG3), and prostate-specific antigen (PSA)	New acronyms defined
Synopsis, 3.1, Figure 2, 4.1, 9.1	Added tumor types: Cohort 7: castration-resistant prostate cancer and Cohort 8: melanoma. Wording throughout the protocol was revised to reflect the addition of Cohort 7 and Cohort 8 as appropriate. Affected sections include: Study population Number of planned subjects Summary of Study Design Study Design and Cohorts – Part A and Part B Primary and secondary objectives Inclusion criteria Determination of Sample Size Statistical methods Efficacy assessments Appendix A Appendix C	To evaluate LV in prostate cancer and melanoma subjects
Synopsis, 3.1	Subjects with the following advanced solid tumors will be enrolled: Cohort 1: SCLC Cohort 2: NSCLC-squamous Cohort 3: NSCLC-nonsquamous Cohort 4: HNSCC Cohort 5: esophageal squamous cell carcinoma (esophageal-squamous) Cohort 6: gastric and gastroesophageal junction (GEJ) adenocarcinoma Cohort 7: CRPC (Part B only) Cohort 8: melanoma (Part B only)	To reflect the addition of 2 subject cohorts to study design
Synopsis, 3.1	The study consists of: • Part A (LV every 3 weeks [q3wk]; Cohorts 1A through 6A): LV administered by IV infusion at a dose of 2.5 mg/kg on Day 1 of each 21-day cycle (see Section 5.1). • Part B (LV q1wk; Cohorts 1B-1.0 mg/kg through 6B-1.0 mg/kg and 1B-1.25 mg/kg through 8B-1.25 mg/kg; starting with Protocol Amendment 1): LV administered by IV infusion	To reflect the addition of 2 subject cohorts to study design and to specify dose level

Section(s)	Change	Rationale
	at a dose of 1.0 mg/kg or 1.25 mg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle (see Section 5.1).	
1.2.4.3, Table 1-3	Added section "Safety data of LV q1wk"	To expand the LV safety profile with recently acquired q1wk safety data from the SGNLVA-001 ongoing study
Synopsis, 2	Added Primary Objective: ● For prostate cancer, investigator-determined PSA response by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria in addition to ORR Added Secondary Objectives: ● For prostate cancer, investigator determined PSA-DOR ● For prostate cancer, investigator determined PSA-PFS	To reflect addition of prostate cancer cohort
Figure 2	Added Cohort 7: Prostate cancer and Cohort 8: melanoma to Figure 2	To reflect the addition of 2 subject cohorts
Figure 3, Appendix B, Appendix C	Changed "Every 12 weeks" to "Every 6 or 12 weeks" for Follow-up in Figure 3: Study Schema Overview and in Appendix B: Schedule of Events for Treatment (Part A) and Appendix C: Schedule of Events for Treatment (Part B)	Clarification for consistency across sections
3.1	Added tumor assessment for prostate cancer subjects: For prostate cancer subjects (Part B, Cohort 7), prostate-specific antigen (PSA) will be assessed every 3 weeks (±3 days). Bone scans will be performed every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter. In addition to PSA and bone scans, prostate cancer subjects with measurable tumor lesions will undergo soft tissue tumor assessment CT/MRI (CT or MRI scan) every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) thereafter according to the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.	To provide plan for tumor assessment in prostate cancer subjects
3.2.3	Updated rationale for selection of q1wk LV doses.	To provide most up to date safety information for LV q1wk dosing
4.1	Added inclusion criteria for Cohort 7, CRPC and for Cohort 8, melanoma.	To provide criteria that must be met for prostate cancer and melanoma subjects to be enrolled

Section(s)	Change	Rationale
Synopsis, 5.1, 5.2.3	For Part B (q1wk dosing), added language to state that the maximum dose of LV is 200 mg per infusion	To align with current guidelines for LV
5.2.4.2, Table 5-4	Provided clarification on allowed concomitant therapy and myeloid growth factors to manage Grade 3 and Grade 4 hematologic and febrile neutropenia toxicities with LV q1wk dosing.	Clarification for consistency across sections
5.3.1	In Part B, primary prophylactic G-CSF is not required but is allowed (see Sections 5.3.2 Allowed Concomitant Therapy and 5.3.3. Myeloid Growth Factors).	Added to ensure consistency with Table 5-4
5.5	Revised wording added: ● Part B: random blood glucose should be checked prior to dosing on Day 1, **8, and 15 of the first 2 cycles. For Cycle 3 and later,** blood glucose **should be checked on Day 1 of each cycle, and** may be checked on Day 8 and/**or** Day 15 **if clinically indicated** for subjects at risk of hyperglycemia.	To clarify random blood glucose testing in Part B (weekly dosing)
6.3.1, 6.3.3, Appendix C	For Part B (q1wk dosing), added multiple study activities to Screening and Treatment Cycle visits. Clarified that CBC with differential, serum chemistry panel and liver function tests, and random blood glucose assessments are only required in Cycle 1 and Cycle 2	Added for prostate cancer subject screening and assessments
6.4, 6.5, 6.6, Appendix C	Added response assessment criteria for prostate cancer subjects (Cohort 7)	To identify prostate cancer subject response assessments
7.2	Added: For prostate cancer subjects, PSA response is defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. The duration of PSA response is defined as the time between the first evaluation at which the response criteria are met and the first documentation of PSA progression. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint.	To define prostate cancer subject response/efficacy assessments
Table 7-1 and Table 7-2	Removed PBMC1 and PBMC2 columns	The probability of using these samples for analysis is low and doesn't justify the cost for continued sample collection
Synopsis, 9.1	Sample size was revised to reflect the additional subjects planned to be enrolled in Cohort 7 and Cohort 8 (revisions shown below for Section 9.1): Up to approximately ~~264~~**324** subjects may be enrolled in the study, including up to 72 subjects in Part A (q3wk dosing), and up to ~~192~~**252** subjects in Part B (q1wk dosing).	To reflect the addition of 2 subject cohorts

Section(s)	Change	Rationale
9.2.2, 9.2.4, 9.2.7	Confirmed PSA Response Rate: Confirmed PSA response rate is defined as the proportion of subjects with a reduction from baseline PSA level of at least 50%, measured twice ≥3 weeks apart. PSA Duration of Response: PSA-DOR is defined as the time from the first documentation of PSA response (subsequently confirmed at least 3 weeks apart) to the first documentation of PSA progression or death due to any cause, whichever comes first. Prostate-Specific Antigen Progression-Free Survival: PSA PFS is defined as the time from the start of study treatment to first occurrence of PSA progression or death, whichever comes first.	New definitions added
9.3.1.7	The PSA evaluable analysis set includes subjects in the prostate cancer cohort who received any amount of study drug and had both baseline and at least one evaluable post baseline PSA measurements.	Definition added
9.3.5.1	For prostate cancer, confirmed PSA response per investigator assessment is another primary endpoint. The confirmed PSA response is defined as a reduction from baseline PSA level of at least 50%, measured twice ≥3 weeks apart. The confirmed PSA response rate and its exact 2 sided 90% CI using the Clopper Pearson method (Clopper 1934) will be calculated.	Primary Efficacy Analysis for prostate cancer subjects added
Appendix F	Edits made in Part A and Part B for G-CSF recommendations	To align with dose modifications tables and Section 5.3
Appendix J	New appendix added as reference	PCWG3 suggested outcome measures for clinical trials in metastatic prostate cancer
Multiple sections	Minor editorial corrections and clarifications made in some sections of the protocol.	Corrections and clarifications

SUMMARY OF SUBSTANTIVE CHANGES IN AMENDMENT 03

Document concerned: SGNLVA-005 Protocol Amendment 03
N° and date of the previous version: 2 dated 27-August-2020
N° and date of the new version: 3 dated 12-October-2020

Note: not all of the changes are reproduced in this table, reference is made to the redlined amendment 3 of the protocol.

Initial Wording	Amended or New Wording	Reason/Justification for Change	Reason of Substantiality
Section concerned: Table 12 Withhold until toxicity is ≤ Grade 2 or baseline[d,e], then reduce dose to the next lower dose level (see Table 11) and resume treatment or discontinue at the discretion of the investigator.[b,c] If dose held >48 hours, may omit and resume dosing at next scheduled dosing day.	Revised wording added: Withhold until toxicity resolves to ≤ Grade 2 or baseline[d,e], then reduce dose to the next lower dose level (see Table 11) 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 11) if treatment is resumed, or discontinue at the discretion of the investigator.	Clarification. The revision aims to improve the clarity of instructions in the management of neutropenia and febrile neutropenia.	Safety related
Section concerned: 7.6.1.5 The sponsor will report all SAEs to regulatory authorities as required per local legislation or regulatory reporting requirements.	Revised wording added: The sponsor will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements.	Updating language to the most current protocol template text and to align with regulatory guidance.	Safety related
Section concerned: 7.6.3 Results of all clinical laboratory tests except pregnancy and PSA tests are to be submitted to iRIS.	Revised wording added: Results of all clinical laboratory tests except pregnancy and PSA tests are to be submitted to iRIS.	Process update. PSA test will not be submitted to iRIS (collected in CRF only).	Process related

SUMMARY OF CHANGES IN AMENDMENT 04

Section(s)	Change	Rationale
Title page	Added Study Director information	Administrative change
Title page	Changed Brief Title to "A Study of Ladiratuzumab Vedotin in Advanced Solid Tumors"	Updated to replace the abbreviation of the drug with the full nonproprietary drug name and to match Brief Title used on clinicaltrials.gov
Protocol Synopsis, Section 9.1	Revised the total number of patients up to approximately 414 subjects	Revised number of patients to reflect addition of Part C
Section 1.2.3	Added additional language on non-clinical toxicology findings including toxicities in testes and ovarian follicles.	Updated to include key toxicology findings since last amendment
Section 1.2.4	Updated SGNLVA-001 study information to include Part F Updated SGNLVA-001 safety and efficacy information to align with the LV IB V09	Part F added to SGNLVA-001 protocol amendment 15 Updated SGNLVA-001 safety and efficacy information to establish rationale for 2q3wk dosing (Section 3.2.5)
Protocol Synopsis, Sections 1.4, 2, 3.1, 3.2.5, 3.2.6, 3.2.7, 4.1, 4.2, 5, 6.4, 7.2, 7.3, 7.6.1.3, 7.6.1.6, 7.6.2, 7.6.3, 7.7, 9.1, 9.3.1.1, Appendix A, Appendix D, Appendix G, Appendix I	Addition of Part C, LV monotherapy and LV + pembrolizumab combination. Part C includes new study arms that apply to Cohort 8 (melanoma) only: **Arm 1:** LV 1.5 mg/kg 2q3wk monotherapy **Arm 2:** LV 1.5 mg/kg 2q3wk + 200 mg pembrolizumab q3wk **Arm 3:** LV 1.25 mg/kg q1wk + 200 mg pembrolizumab q3wk Updated Figure 2 and Figure 3 with new study design. Added new Sections 3.2.5 and 3.2.6 to provide a rationale for Part C and new 2q3wk schedule in Arm 1 and Arm 2. Updated Sections 3.2.5 and 3.2.6 to reflect Part C addition. Added new Section 6.4 and Appendix D to outline study activities for Part C. Updated Appendix A and Appendix G to include Part C.	Part C of SGNLVA-005 is testing the safety and efficacy of LV monotherapy and LV + pembrolizumab combination therapy in Cohort 8 (melanoma)

Section(s)	Change	Rationale
	Updated Section 7 and Section 9 to include study assessments and changes to statistical methods including continuous monitoring of the benefit-risk profile for Part C. Added Appendix I. Response assessments for Arm 2 and Arm 3 will use iRECIST criteria in addition to RECIST v1.1 to guide treatment decision-making.	
Sections 1.3, 3.2.7, 5.3, 5.4.4.1, 5.5.1.2, 5.5.1.3, 5.5.2.2, 5.5.3, 5.5.4	Addition of pembrolizumab drug information: Added Section 1.3 which includes background for pembrolizumab Added Section 3.2.7 as rationale for pembrolizumab dose. Updated Section 4 to include inclusion/exclusion criteria for Part C pembrolizumab arms. Added Section 5.3 to include pembrolizumab drug information, administration, dose modification, and other safety information. Updated Section 5.4 to include concomitant therapy information for pembrolizumab. Update Section 5.5 to include AE information for pembrolizumab.	Added for Part C pembrolizumab combination therapy (Arm 2 and Arm 3)
Sections 7.4, 7.4.1	Added additional detail on biomarkers to be assessed from blood samples	Additional details added to more accurately convey biomarker assessments that will be performed
Section 7.6.1.2	Updated time period for reporting pregnancy to the Drug Safety Department from “within 48 hours” to “within 24 hours”	Update to match current Seagen Inc. policy
Throughout protocol	Minor editorial corrections and clarifications made in some sections of the protocol.	Corrections and clarifications