PrECOG Protocol Number: PrE0504

A Phase I/II Study of Glembatumumab Vedotin in Patients with gpNMB-Expressing, Advanced or Metastatic Squamous Cell Carcinoma of the Lung

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PHASE I & PHASE II SCHEMA

Phase I Schema

Phase I Only: Prior to discussing protocol entry with the patient, call the assigned PrECOG Project Manager to ensure a place on the protocol is open to the patient. Eligibility Criteria Checklist must be sent to the PrECOG PM/designee for review and approval prior to subject registration. Additional contact details are provided in the Study Reference Manual.

REGISTRATION →

Dose Level/ Cohort	Glembatumumab Vedotin IV every 3 weeks over 90 minutes[1]
-1[3]	1.3 mg/kg
1[2,4]	1.9 mg/kg

→ **Treatment until Disease Progression or Intolerance**

1 DLT is defined per Section 6.1.7 occurring through the end of the second treatment cycle (i.e., by day 42 (±3) days).
2 Amendment 2: A maximum of three additional patients were treated on Dose Level/Cohort 1 (1.9 mg/kg) for 9 patients at this dose level to verify the safety of this dosage regimen (Section 5.1.1 for details).
3 Three patients completed treatment on Dose Level/Cohort -1 with no DLTs.
4 We will re-escalate to Dose Level/Cohort 1. An additional 3-6 patients will be treated on Dose Level 1 (up to 15 total).

Phase I = maximum of 18 patients

Phase II Schema

REGISTRATION →

Stage	Glembatumumab Vedotin IV every 3 weeks over 90 minutes	Patients (n)
Stage 1	MTD[1]	20
Stage 2	MTD[1]	15

→ **Treatment until Disease Progression or Intolerance**

1 MTD as determined during the dose-escalation phase.

In Stage 1, approximately 20 eligible, treated patients will be enrolled. If ≥ 2 patients achieve a tumor response [Partial Response (PR) or Complete Response (CR)]; an additional 15 eligible, treated patients will be enrolled in Stage 2, for a maximum total of 35 eligible, treated patients. To assure sufficient eligible, treated patients, up to 2 additional patients may be enrolled (total of 37 patients). There will be rigorous toxicity monitoring in Phase II – please see Statistical Considerations (Section 10.2.2.1) for details.

Phase I & Phase II treatment should begin within 10 working days of registration.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ACS	American Cancer Society
ADC	Antibody-Drug Conjugate
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Receptor Tyrosine Kinase
ALT (SGPT)	Alanine Transaminase (Serum Glutamic Pyruvate Transaminase)
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
CFR	Code of Federal Regulations
CI	Confidence Interval
CR	Complete Response
CNS	Central Nervous System
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DC-HIL	Dendritic Cell-Heparin Integrin Ligand
DCTD	Division of Cancer Treatment and Diagnosis
DHHS	Department of Health and Human Services
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EST	Eastern
FDA	Food and Drug Administration
FNA	Fine Needle Aspirate
FSH	Follicle-Stimulating Hormone

Abbreviation	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
gpNMB	Glycoprotein NMB
HGFIN	Hematopoietic Growth Factor Inducible Neurokinin-1 type
HIPAA	Health Insurance Portability and Accountability Act
IC	Investigator's Choice
ICH	International Conference on Harmonization
IgG_2	Immunoglobulin G, Subclass 2
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
IV	Intravenous
Kg	Kilogram
LCMS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliters
MMAE	Monomethylauristatin E
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
n	number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (of the United States)
NE	Inevaluable
NIH	National Institutes of Health
NR	Not Reported
NSCLC	Non-Small Cell Lung Carcinoma
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival

Abbreviation	Definition
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Response
q3w	Every 3 Weeks
RBC	Red Blood Count
RECIST	Response Evaluation Criteria for Solid Tumors
RNA	Ribonucleic Acid
ROC	Receiver Operating Curve
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SOPs	Standard Operating Procedures
SRM	Study Reference Manual
TA	Total Antibody
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
ULN	Upper Limit of Normal
vc	Valine-Citrulline
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Count

1. PROTOCOL SYNOPSIS

Protocol Number	PrE0504
Title	A Phase I/II Study of Glembatumumab Vedotin in Patients with gpNMB-Expressing, Advanced or Metastatic Squamous Cell Carcinoma of the Lung
Investigational Treatment	[redacted]
Indication	Patients with unresectable Stage IIIB or Stage IV, gpNMB-expressing squamous cell carcinoma (SCC) of the lung who have failed a prior platinum-based chemotherapy regimen.
Number of Patients	Approximately 55 patients will be enrolled
Number of Study Centers	Approximately 10 study centers will participate
Objectives	**Primary:** • Phase I: To evaluate the safety and tolerability and determine the Maximum Tolerated Dose (MTD) of glembatumumab vedotin in patients with advanced gpNMB-expressing SCC of the lung. • Phase II: Determine the anti-tumor activity, as assessed by objective response rate (ORR) in accordance with RECIST 1.1, of the MTD of glembatumumab vedotin in patients with advanced gpNMB-expressing SCC of the lung. **Secondary:** • To further characterize the safety of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung. • To further evaluate the anti-cancer activity of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung, as measured by duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS). **Exploratory:** • To investigate if the anti-cancer activity of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung is dependent upon the degree of gpNMB expression in tumor tissue. • To examine pharmacodynamic effects of treatment, including tumor immune cell infiltrate type and number; localization of glembatumumab vedotin, CR011 or Monomethylauristatin E (MMAE) at the tumor site; soluble mediators and/or gpNMB expression levels in tumor tissue; and analysis of peripheral blood cell subsets. • To further characterize the pharmacokinetics and immunogenicity of glembatumumab vedotin in this patient population.
Overview of Study Design	This is an open-label, single arm study of glembatumumab vedotin in patients with unresectable, Stage IIIB or IV, gpNMB-expressing SCC of the lung who have failed a prior platinum-based chemotherapy regimen. This study will include a dose-escalation phase followed by a 2-stage Phase II expansion, as follows:

Study Phase	Dose Level/ Cohort	Glembatumumab Vedotin Dose (mg/kg)	Patients (n)
Phase I Dose-Escalation	-1[2]	1.3	3
	1[1,3]	1.9	9 already treated; 3-6 more to be added
Phase II	Stage 1	MTD*	20
	Stage 2	MTD*	15

[1] Amendment 2: A maximum of three additional patients were treated on Dose Level/Cohort 1 (1.9 mg/kg) for 9 patients at this dose level to verify the safety of this dosage regimen (Dose Escalation Phase below and Section 5.1.1 for details).

[2] Three patients completed treatment on Dose Level/Cohort -1 with no DLTs.

[3] We will re-escalate to Dose Level/Cohort 1. An additional 3-6 patients will be treated on Dose Level 1 (up to 15 total).

* MTD as determined during the dose-escalation phase

All patients will be seen in the clinic at scheduled intervals during the treatment phase of the study. Patients will not be permitted to have concurrent chemotherapy, immunotherapy or other experimental therapies during study treatment.

Patients will receive glembatumumab vedotin in an open-label fashion, once every three weeks (q3w) by 90-minute intravenous (IV) infusion, until disease progression or intolerance. Tumor assessments will be performed every six (±1) weeks for six months, and every nine (±2) weeks thereafter, until progression. Tumor response will be assessed by the investigator in accordance with RECIST 1.1 guidelines (Eisenhauer, Therasse et al. 2009). Patients who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies.

Dose-Escalation Phase:

Original Plan:

For the dose-escalation, the starting dose of glembatumumab vedotin will be 1.9 mg/kg q3w (Cohort 1). This dose level is based upon the previously identified therapeutic dose of 1.88 mg/kg q3w, with rounding to 1.9 mg/kg for reasons of practicality and feasibility in preparation of the infusion. Notably, this rounded dose remains below the “intermediate” dose level of 2.0 mg/kg q3w, which was previously deemed tolerable in the Phase I/II melanoma study, CR011-CLN-11.

Initially, three patients will be enrolled to Cohort 1. In the event of 1 dose-limiting toxicity (DLT), the cohort will be expanded to 6 patients. In the event of ≥ 2 DLTs, the cohort will have exceeded the MTD, and the dose will de-escalate. In this case, 3 patients will be enrolled to Cohort -1 and the same DLT evaluation rules will apply, such that 1 DLT will require expansion to 6 patients; this dose level will be deemed the MTD if DLT occur in 0/3 or ≤ 1/6 patients; and the study will cease if ≥ 2 DLTs occur at dose level -1.

Dose escalation from Cohort 1 to Cohort 2 may proceed if three patients in Cohort 1 complete the DLT observation period with 0 DLTs, or if six patients in Cohort 1 complete the DLT observation period with 0 or 1 DLTs. The MTD for the dose-

	escalation phase will be the highest dose-level where 0/3, or ≤ 1/6 patients in a cohort experienced a DLT. **Amendment #2.0:** As of February 14, 2017; of the 6 patients whom were enrolled on Cohort 1 (1.9 mg/kg), 1 DLT was observed (Grade 5 respiratory failure deemed as possibly related to study drug [complicated by progressive disease at same time]). The deaths of two subjects were reported and appear most likely related to progressive disease and unrelated to the drug. However, dose escalation to Cohort 2 seemed premature. To further assess the safety signal and not put either subjects or the drug in jeopardy, it was PrECOG's decision to modify the Phase I portion and treat a maximum of 3 additional patients on Cohort 1 (1.9 mg/kg) for up to 9 patients at this dose level to verify the safety of this dosage regimen. If any of the 3 additional patients experience a DLT, the dose will de-escalate to Cohort -1. If none of the additional 3 patients experience a DLT, dose escalation may proceed from Cohort 1 to Cohort 2. The same DLT evaluation rules will apply as noted above. A second DLT was observed on Cohort 1. Patient experienced Grade 3 treatment-related pruritus requiring hospital admission. Although a vital organ was not involved, due to the extent and intensity of the treatment required for pruritus, it was considered a DLT. Dose was de-escalated to Dose Level -1. **Amendment #3.0:** Three patients were enrolled to Dose Level -1 with no DLTs during the 42 day assessment period. Given the fact one of the previously reported DLTs at 1.9 mg/kg was complicated by the patient have progressive disease at the same time, and the other (pruritus) is a known and generally manageable adverse event associated with glembatumumab vedotin, it is reasonable to re-escalate, and re-explore the safety of the 1.9 mg/kg cohort. The protocol is being amended to include a plan to re-escalate to Dose Level 1. Upon re-escalation to Dose Level 1, 3 patients will be treated. This dose level will be deemed unsafe if at least 2 patients among the first 3 patients enrolled experiences a DLT, and Dose Level -1 will be deemed the MTD. If no DLTs are observed among the first 3 patients **or** if 1/3 patients experiences a DLT then we will enroll 3 more patients. This dose level will be determined to be the MTD in the event that <2/6 patients treated at Dose Level 1 experience DLT. If ≥ 2/6 patients experience DLT at Level 1, then Dose Level -1 will be declared the MTD. Note that Dose Level 2 is no longer part of the study effective with this amendment. The DLT evaluation period for determination of the appropriateness of dose-escalation will be through the end of the second treatment cycle. Patients who discontinue safety follow-up before day 42 (±3 days) for reasons other than DLT will be replaced. Any DLT at any time point during the study must be reported to PrECOG (or designee) as soon as possible, but no later than 24 hours following the site becoming aware of the event, and PrECOG will distribute such notification to all participating sites within 24 hours of notification. Site teleconferences between PrECOG and all participating sites will be held at frequent intervals and prior to dose-escalation to each cohort during the dose-escalation phase. PrECOG study personnel, including but not limited to the Study Chair(s), statistician, medical monitor and participating investigators, as applicable, will review toxicities from the current cohort during the site teleconferences before initiating enrollment into the next planned dose cohort.

	DLT Definition: For escalation and MTD decisions, DLT is defined as any of the following conditions occurring through the end of the second treatment cycle (i.e., by day 42 (±3) days): • Grade 3 or 4 non-hematological drug-related toxicity not resolving to Grade 2 or less within 72 hours of initiation of supportive care. Exceptions to this criterion include asymptomatic lab abnormalities deemed not clinically significant and other toxicities of non-vital organs after discussion with PrECOG/medical monitor. • Grade 4 neutropenia lasting >5 days. • Grade 3 or higher neutropenia with associated fever >38.1˚C (100.5˚F). • Grade 4 thrombocytopenia. • Grade 3 irreversible peripheral sensory neuropathy that does not resolve or return to baseline status within 4 weeks of last dose of study drug. • Grade 4 neuropathy of any duration. • Anaphylaxis or Grade 4 infusion-related reaction. • Grade 5 toxicities considered possibly, probably, or definitely related to treatment. • Any treatment-related toxicity requiring permanent discontinuation of glembatumumab vedotin. **Phase II:** Following determination of the MTD, a Phase II study portion will enroll up to 35 eligible, treated patients to further assess the safety and efficacy of glembatumumab vedotin. Patients who discontinue study for reasons other than symptomatic deterioration or death prior to a radiographic assessment will be considered unevaluable and will be replaced. Enrollment to the Phase II study portion will proceed according to a two-stage trial design (Simon 1989), so that enrollment may terminate early if the results are not sufficiently promising to warrant further study. In Stage 1, approximately 20 eligible, treated patients will be enrolled. If ≥ 2 patients achieve a tumor response (Partial Response [PR] or Complete Response [CR]), an additional 15 eligible, treated patients will be enrolled in Stage 2, for a maximum total of 35 eligible, treated patients. To assure sufficient eligible, treated patients, up to 2 additional patients may be enrolled (total of 37 patients). Additionally, we will monitor for the incidence of Grade 5 events. In particular, we will monitor the Grade 5 event rate among the first stage accrual of 20 patients. All Grade 5 events deemed at least possibly related to treatment as well as any Grade 5 events occurring within 3 weeks of the first dose (Cycle 1) regardless of attribution are included as 'events' for the purpose of monitoring. See Section 10.2.2.1 for details.
Study Treatment Dosing and Administration	Glembatumumab vedotin will be administered on Day 1 of repeated 21-day cycles, as a 90-minute IV infusion using a 0.22 micron in-line filter. In the dose escalation phase, the starting dose for each patient is based on cohort assignment; Cohort 1 (dose level 1) will be 1.9 mg/kg. In the Phase II study portion, the starting dose will be the MTD established in the dose escalation phase. Treatment may be delayed for up to three weeks (i.e., 1 cycle) to allow sufficient time for recovery from treatment-related toxicities. If a delay greater than three weeks is required, the Investigator should confer with PrECOG to determine the appropriateness of continued treatment. Prior to each treatment with glembatumumab vedotin, the following conditions must be met. • The absolute neutrophil count (ANC) must be ≥ 1500/mm^3 and platelets ≥ 100,000/mm^3 prior to the start of each cycle. Growth factor support is permitted, and should be administered with consideration to the American Society of Clinical

	Oncology (ASCO) guideline on the use of hematopoietic colony stimulating factors (Smith, Khatcheressian et al. 2006). • Drug-related non-hematological toxicities must have improved to baseline or NCI-CTCAE ≤ Grade 2. Exceptions to this criterion include alopecia and other toxicities of non-vital organs after discussion with PrECOG. Dose adjustments in individual patients for toxicity are permitted. Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. A maximum of two dose reductions are allowed. If a patient requires more than two dose reductions or reduction below the 1.0 mg/kg dose, they should be discontinued from treatment. Patients experiencing the following conditions require dose reduction: • DLT - Any toxicity defined as DLT (Section 6.1.7) occurring at any time during the course of treatment. • Patients who develop Grade 2 or 3 neuropathy will have dosing held until neuropathy improves to Grade 1 or baseline, and will be restarted with a dose reduction. Patients with Grade 4 neuropathy should have treatment discontinued permanently. • Other events that, in the opinion of the treating investigator, warrant dose modification.
Eligibility Criteria	***Phase I Only: Eligibility Criteria Checklist must be sent to the PrECOG PM/designee for review and approval prior to subject registration.** **Inclusion Criteria:** 1. Read, understood, and provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures. 2. Male or female patients with metastatic, histologically- or cytologically-confirmed unresectable Stage IIIB or IV non-small cell lung cancer (NSCLC) of squamous histology (Staging per American Joint Committee on Cancer [AJCC], Edition 7). Mixed histology adenosquamous NSCLC will also be permitted. 3. Experienced progression/recurrence of disease during or subsequent to the most recent anti-cancer regimen. 4. Any number of prior lines of systemic therapy may have been received for advanced (recurrent, locally advanced, or metastatic) SCC of the lung, but at least one must have been a platinum-based chemotherapy regimen. Platinum therapy may be given on-label or as part of a clinical trial. 5. Lung cancer confirmed to express gpNMB, as assessed by immunohistochemistry at a central lab (using expression in ≥ 5% of tumor epithelial cells as a cut-off for positivity). This can be tested on archived tissue if available, although preferred tumor specimen is a biopsy after the most recent therapy. **NOTE:** Additional samples from previous collection dates should also be submitted when feasible. Submitted cytology samples such as pleural effusions, bronchial washings or fine needle aspirates (FNA) will be used to evaluate feasibility of gpNMB expression analysis and to investigate correlations with other samples for the patient, but they will not be used for determination of study eligibility. For patients with multiple samples submitted, eligibility will be based on the most recently obtained sample, or, if obtained on the same date, the sample with the highest level of gpNMB expression. However, in the event that disparate results are obtained for samples received within a similar timeframe (i.e., within a 6-month period), the medical monitor may be consulted for determination of eligibility.

6. Age ≥ 18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (Appendix 2).
8. Measurable disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (Appendix 3). Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.
9. Resolution of all toxicities related to prior therapies to ≤ NCI-CTCAE Grade 1 severity, except for alopecia, vitiligo, or endocrinopathies on replacement therapy.
10. Adequate bone marrow function as assessed by absolute neutrophil count (ANC) ≥ 1500/mm^3; hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm^3.
11. Adequate renal function as assessed by serum creatinine ≤ 2.0 mg/dL; or calculated (Cockcroft and Gault Formula; Appendix 4) or 24-hour urine creatinine clearance >40 mL/min.
12. Serum albumin ≥ 3 g/dL.
13. Adequate liver function as assessed by total bilirubin ≤ 1.5x upper limit of normal (ULN), and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5x ULN (≤ 5.0x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.

    NOTE: The liver is a route of clearance for MMAE. Patients with mild hepatic impairment are excluded from Phase I (the dose escalation portion) to minimize the influence of hepatic impairment on tolerability and dose selection because a lower dose is recommended for other ADCs with a vc-MMAE moiety. **See the acceptable liver function parameters for Phase I defined above.** In Phase II (the dose expansion portion) a lower starting dose for patients with mild hepatic impairment will be determined based on the MTD recommended from the Phase I portion of this trial. **The acceptable liver function parameters will be redefined for Phase II.**
14. Both male and female patients of childbearing potential enrolled in this trial must use adequate birth control measures during the course of the trial and for at least one month after discontinuing study drug. Adequate birth control measures are defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, or intrauterine device), implants, injectables, combined oral contraceptives, sexual abstinence (abstinence from intercourse during the ovulation period), or vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.
15. Willing to provide blood samples for research purposes (Section 11.2).

Exclusion Criteria:

1. Received glembatumumab vedotin (CR011-vcMMAE; CDX-011) or other MMAE-containing agents previously.
2. Chemotherapy within 21 days or at least 5 half-lives (whichever is shorter) prior to the planned start of study treatment; radiation outside the thorax within 14 days prior to the planned start of study treatment or thoracic radiation; antibody based therapy or investigational therapy within 28 days prior to the planned start of study treatment.
3. Neuropathy >NCI-CTCAE Grade 1.
4. Subjects with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin. Compounds of similar composition include Auristatin PHE as an anti-fungal agent, Auristatin PE (TZT-1027, Soblidotin, NSC-654663) as an anti-tumor agent and Symplostatin 1 as an anti-tumor agent.

	5. Known brain metastases, unless previously treated and patients are neurologically returned to baseline except for residual signs and symptoms related to Central Nervous System (CNS) treatment and CNS lesions are not progressive in size and number for 4 weeks. 6. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, and congestive heart failure (New York Heart Association (NYHA) Class 3 or 4 [Appendix 5]) related to primary cardiac disease, a history of a serious uncontrollable arrhythmia despite treatment, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry. 7. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. **NOTE:** Microscopic examination of urinalysis is required during screening. If urinary infection is suspected, a negative urine culture is required prior to enrollment. 8. Subjects on immunosuppressive medications such as azathioprine, mycophenolate mofetil, cyclosporine or require chronic corticosteroid use (defined as ≥ 3 months of prednisone dose equivalent of ≥ 10 mg). 9. The MMAE component of glembatumumab vedotin is primarily metabolized by CYP3A. Patients taking strong CYP3A inhibitor and inducers are excluded in Phase I (the dose escalation portion), to minimize the effect of these modulators on exposure, tolerability and dose selection (http://medicine.iupui.edu/clinpharm/ddis/main-table/). 10. History of other malignancy except for adequately treated basal or squamous cell skin cancer, curatively treated in situ disease, or any other cancer from which the patient has been disease-free for ≥ 2 years. 11. Pregnant or breast-feeding women. 12. Subjects must not be on home oxygen therapy (intermittent or continuous). 13. Any underlying medical condition that, in the Investigator's opinion, will make the administration of study treatment hazardous to the patient, or would obscure the interpretation of adverse events.
Criteria for Evaluation	**Safety Evaluations:** Safety will be assessed by vital sign measurements, clinical laboratory tests, ECGs, physical examinations and the incidence and severity of adverse events (graded according to NCI-CTCAE V4.0.). **Anti-Tumor Activity Evaluations:** Anti-tumor activity will be assessed based on ORR, DOR, PFS and OS. Tumor response and progression will be defined by the investigator, according to RECIST 1.1 criteria. **Immunogenicity:** Patients will be monitored for the development of anti-glembatumumab vedotin and anti-CR011 antibodies, and whether these antibodies are neutralizing. **Pharmacokinetics (PKs):** Concentration of the antibody-drug conjugate (ADC), total antibody (TA) and free MMAE will be determined using Good Laboratory Practices (GLP) compliant enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The impact of circulating gpNMB levels on pharmacokinetic parameters may also be examined.

	Pharmacodynamics: Pharmacodynamic parameters will be evaluated via assessment of post-treatment tumor tissue obtained via voluntary biopsy or resection and/or blood samples. Parameters evaluated may include localization of glembatumumab vedotin, CR011 or MMAE at the tumor site and/or gpNMB levels on cells in blood and tumor tissue, as well as evaluation of tumor infiltrating and peripheral leukocytes, circulating tumor cells and other immune response cells of interest. Soluble gpNMB levels in circulation may also be examined.
Statistical Methods	**Sample Size Considerations:** ***Escalation Phase:*** **Refer to Section 5.1.1 for details.** Three to 6 patients will be enrolled in each dose cohort based on Phase I dose escalation scheme as described above in the Overview of Study Design Section. (Dose Level 1 will enroll up to 15 patients as noted above and in Section 5.1.1). Each patient will participate in only 1 dose cohort. The total number of patients to be enrolled in the dose escalation phase is dependent upon the observed safety profile after 2 cycles, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the maximum tolerated dose (MTD). A starting sample size of 3 patients per dose cohort, expanding to 6 patients in the event of a marginal dose-limiting toxicity (DLT) rate (33%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 83% chance that dose escalation would be halted in a given cohort. ***Phase II Study Portion:*** In the Phase II study portion, the safety and preliminary antitumor activity of glembatumumab vedotin at the selected dose will be explored. Up to 35 eligible, treated patients may be enrolled according to a single-arm Phase II trial design with ORR as the primary endpoint. The Phase II study portion will be carried out in 2 stages so that enrollment can terminate early in the event that glembatumumab vedotin is not sufficiently active in this patient population. A true ORR of 20% is hypothesized. A response rate of less than 5% is not considered clinically meaningful. The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on Simon's 2-stage design, with 90% power and 1-sided significance level of less than 10%. Based on the above considerations, 20 eligible, treated patients will be enrolled (first stage): if ≤ 1 patient achieves a CR or (PR), then the trial will stop for futility; otherwise, 15 additional eligible, treated patients will be enrolled in the second stage, for a total of 35 eligible, treated patients. The regimen will be considered worthy of further study if 4 or more responses are observed among 35 eligible, treated patients. To assure sufficient eligible, treated patients, up to 2 additional patients may be enrolled (total of 37 patients). The primary endpoint of ORR will be estimated by the crude proportion of eligible, treated patients with best overall response of confirmed CR or PR, along with a 2-sided 90% Confidence Interval (CI) if the study stops early; if the study proceeds to a second stage then the CI will be computed using the methodology of Atkinson and Brown. Secondarily, ORR, inclusive of confirmed and unconfirmed PR and CR, will also be estimated.

	DOR will be calculated for patients who achieve a confirmed CR or PR. DOR is defined as the time from the start date of the confirmed response to the first date that recurrent or progressive disease or death is objectively documented. PFS is defined as the time from the date of the first dose of study drug to the earliest of documented disease progression or death without prior progression. Patients not experiencing an event will be censored at their last adequate disease assessment date. OS is defined as the time from the date of the first dose of study drug to the date of death (whatever the cause). Patients not experiencing an event will be censored at the last follow-up date. DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 90% confidence intervals (CIs) calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up. PFS rate and OS rate at selected landmarks and corresponding 90% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 90% CI. Waterfall plots will be used to depict graphically the maximum decrease from baseline of target lesions. The correlation between gpNMB expression and clinical outcomes will be explored. The analysis of tumor response and PFS will be based on tumor response assessments performed by the investigator according to standardized, objective response criteria (RECIST 1.1). In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an independent review committee (IRC), blinded to investigator assessments.

2. SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Assessments[1]

Visit	Screening[2]		Treatment Visits[3]					Disease Assessment Visit[6]	Survival Assessment[7]
		Cycle 1/ Day 1	Cycle 1/ Day 8[4]	Cycle 1/ Day 15[4]	Cycle 2/ Day 1	Cycle 3 onward/Day 1	End of Treatment[5]		
Visit Window	*Day -28 to Day -1*		*+/-1 days*	*+/-1 days*	*+/-3 days*	*+/-3 days*	*Within 28 days post-dosing*	*Every 6 (±1) weeks for 6 months then every 9 (±2) weeks thereafter*	*Every 12 (±2) weeks until study closure*
Informed Consent/HIPAA	X								
Tumor Tissue[8]	X[9]						X[10]		
Medical/Surgical History[11]	X	X							
Physical Examination[12]	X	X[13]	X	X	X	X	X		
Vital Signs[14]	X	X[13]	X	X	X	X	X		
ECOG Performance Status	X	X[13]			X	X	X		
Electrocardiogram (ECG)	X						X		
Pregnancy Test[15]	X	X[13]							
Hematology[16]	X	X[13]	X	X	X	X	X		
Blood Chemistry[16]	X	X[13]	X	X	X	X	X		
Urinalysis[16]	X	X[13]			X	X	X		
Immunogenicity[17,18]		X				X[17]	X[17]		
PBMC Collection[18,19]		X			X		X		
Routine PK Sample Collection[18,20]		X[20]	X	X	X[20]	X[20]	X		
Disease Assessment[21]	X							X	
Administration of Study Treatment[22]		X			X	X			
Survival Status									X
Concomitant Medication Review[23]	X	X	X	X	X	X	X		
Adverse Event Monitoring[24]		X	X	X	X	X	X		X[25]

(footnotes on next page)

Table 1 - Footnotes:

1. A delay in study treatment or performance of study assessments due to holidays, weekends, inclement weather or other unforeseen circumstances will be permitted and not considered a protocol violation. However, such cases should be discussed with PrECOG to reach consensus on subsequent scheduling.
2. **Phase I: Prior to discussing protocol entry with the patient, call the assigned PrECOG Project Manager to ensure that a place on the protocol is open to the patient (Section 5.2.4). Eligibility Criteria Checklist must be sent to the PrECOG PM/designee for review and approval prior to subject registration. Site will receive a confirmation of approval. Once confirmation of approval is received subject can be registered.** No study procedures will be performed prior to receipt of signed Informed Consent. However, assessments performed according to standard of care prior to receipt of Informed Consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.
3. Patients will receive glembatumumab vedotin (on a three-week cycle) until intolerance, progression of disease, or any of the other criteria for discontinuation of study treatment (Section 5.2.6) are met.
4. The Cycle 1/Day 8 and Cycle 1/Day 15 visit is only required for patients treated in the Phase I, dose-escalation phase.
5. The End of Treatment Visit should be performed within 28 days after last dose of study treatment and prior to initiation of alternate therapies.
6. Disease assessments will be performed every 6 weeks (±1 week) for 6 months and every 9 weeks (±2 week) thereafter, until documented progression of disease or initiation of alternate anticancer therapies. If a partial or complete response is noted, a follow-up radiographic assessment must be done no sooner than 28 days later to confirm response. Patients who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies. If surgical intervention or localized radiation are indicated (either for palliation or down-staging of previously non-resectable tumor), these interventions should be avoided if clinically feasible until after the 12 week response assessment. Prior to any intervention (such as surgical resection, palliative radiation or alternate anti-cancer therapy), every effort should be made to perform a tumor response assessment in order to document progression and/or confirm an objective response. Patients who undergo surgical resection or radiation in the absence of progression will have glembatumumab vedotin temporarily withheld during treatment and for at least 21 days after completion of surgical resection or radiation treatment or until patient has recovered from any adverse events resulting from the surgical or radiation intervention before restarting treatment with glembatumumab vedotin. Patients may continue to receive study treatment until remaining lesions meet criteria for progression of disease.
7. Subsequent to the End of Treatment Visit, all patients with disease progression will be followed at 12 (±2) week intervals until study closure. Patients who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies. For patients who continue to be seen for disease assessments, the survival contact may occur at these visits (i.e., at a 6 or 9 week interval, as applicable). Otherwise, these visits may be performed by telephone.
8. Assessment of gpNMB expression (by IHC) at a central laboratory **(approximately 5 working day turnaround)**; additional analyses to be performed may also include gpNMB expression by reverse transcriptase polymerase chain reaction (RT-PCR), examination of tumor markers using IHC or other molecular analyses, evaluation of tumor infiltrating leukocyte populations, and localization of glembatumumab vedotin, CR011 or MMAE at the tumor site in post-treatment samples (Section 11.1). Sample collection, processing and shipping instructions will be provided.
9. Tumor specimen(s) used to determine gpNMB status and eligibility may be obtained at any point in the course of disease; preferred tumor specimens are those obtained in the setting of advanced (recurrent, locally advanced or metastatic) disease and subsequent to the last anti-cancer regimen received.. Formalin-fixed paraffin-embedded (FFPE) diagnostic tumor tissue block(s) or 10-20 FFPE slides plus H&E slide from a tumor tissue block will be required (Section 11.1). **NOTE:** Additional samples from previous collection dates should also be submitted when feasible. Submitted cytology samples such as pleural effusions, bronchial washings or fine needle aspirates (FNA) will be used to evaluate feasibility of gpNMB expression analysis and to investigate correlations with other samples for the patient, but they will not be used for determination of study eligibility. Samples may be submitted and tested at any time prior to or during the 28-day window for screening, provided that the patient has signed an appropriate consent (either a tumor tissue-specific consent or full study consent). Samples may be submitted for patients who are not yet fully eligible for the study at the investigators discretion.
10. In the event of tumor resection, biopsy, or cytological sample collection anytime during treatment or following tumor progression, submission of these tissue samples for central analysis is strongly encouraged.

11. Medical/Surgical history includes demography, race, ethnicity, cancer history, previous therapy, and pre-existing diseases. At Cycle 1, Day 1, history is updated with any adverse events occurring prior to administration of study drug.
12. Complete physical exam should be performed at screening; thereafter, symptom-directed exams are acceptable.
13. Assessments do not need to be repeated if completed within the previous 72 hours as part of the screening assessment. **NOTE:** Microscopic examination of urinalysis is required during screening. If urinary infection is suspected, a negative urine culture is required prior to enrollment.
14. Vital signs to include height (at screening only), weight, respiration, pulse, temperature, and resting systolic and diastolic blood pressure. On glembatumumab vedotin dosing days, vital signs should be assessed pre-infusion, at 45 (±15) minutes during the infusion, and within one-half hour following completion of the infusion. (**Note:** Weight is only assessed once per visit.)
15. Serum or urine pregnancy test only for women of childbearing potential. Patients of non-childbearing potential include those who are surgically sterilized or post-menopausal with absence of menses for at least 1 year. However, women <60 with therapy-induced amenorrhea will require a pregnancy test unless additional evidence (oophorectomy or serial measurement of follicle-stimulating hormone (FSH) and/or estradiol) are available to ensure postmenopausal status.
16. Laboratory assessments must include the following, when indicated. Hematology results must be reviewed prior to dosing.

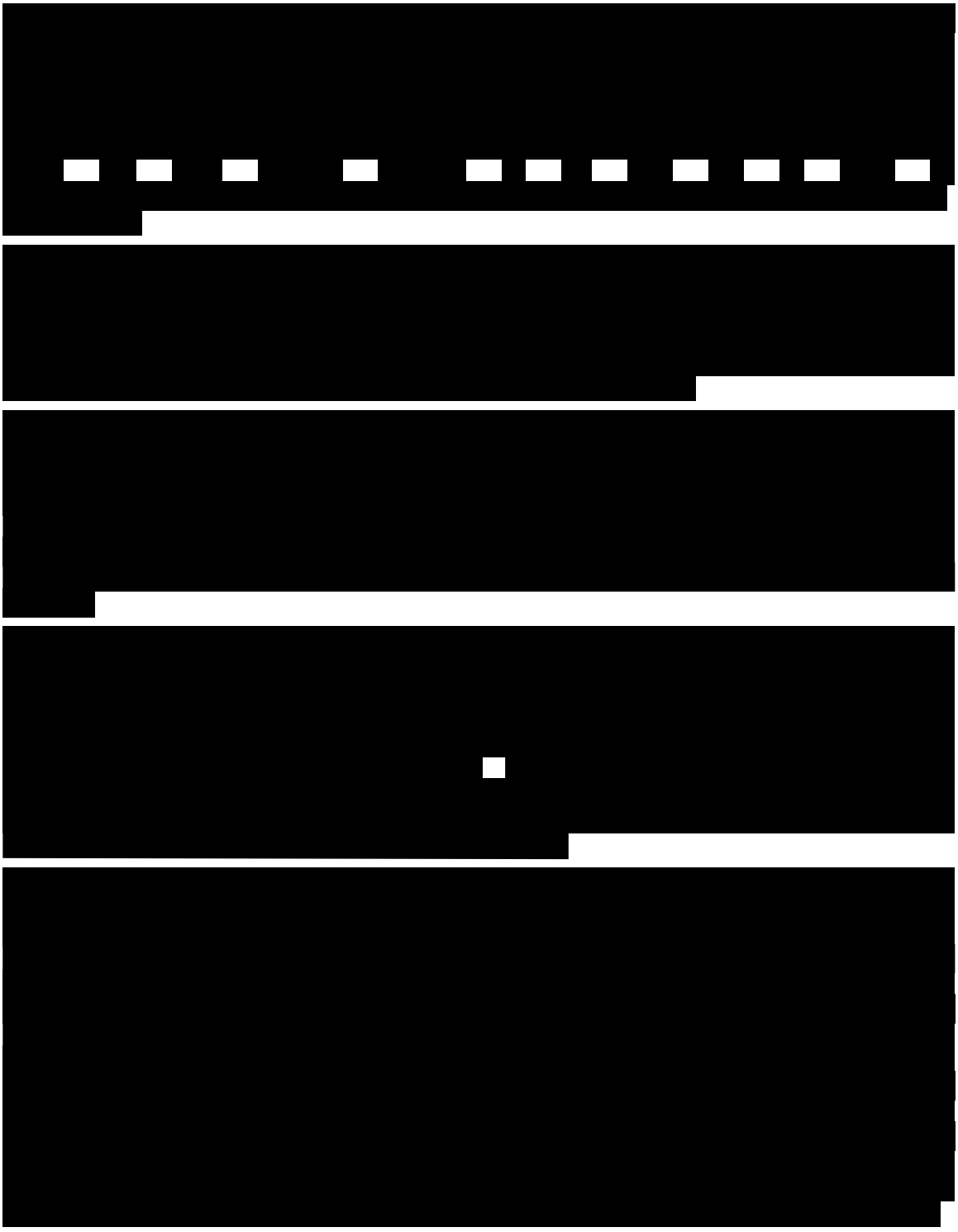
Hematology:	**Clinical Chemistry:**	**Urinalysis**
Hemoglobin	Sodium	PH
Hematocrit	Potassium	Protein
Mean corpuscular volume (MCV)	Chloride	Glucose
RBC (Red Blood Count)	Glucose (nonfasting)	Specific gravity
WBC (White Blood Count)	Blood urea nitrogen (BUN)	Blood
Platelets	Creatinine	
Differential:	Calcium	
Neutrophils	Phosphate	
Lymphocytes	Alkaline phosphatase	*Microscopic examination must be performed at baseline and, if clinically indicated, at subsequent visits.*
Monocytes	Alanine transaminase (ALT/SGPT)	
Eosinophils	Aspartate transaminase (AST/SGOT)	
Basophils	Total protein	
Differential should be reported consistently throughout the study as either an absolute count (preferred) or as a percentage.	Albumin	
	Lactate Dehydrogenase (LDH)	
	Total Bilirubin	

17. 6 mL blood sample (red top tube) for serum for immunogenicity will be collected prior to dosing on Day 1 of "odd" cycles (i.e., Cycles 3, 5, 7, etc.) and End of Treatment. Analysis may also include circulating soluble gpNMB levels or other soluble molecules (Section 11.2).
18. Analyses will be performed centrally. Sample collection, processing and shipping instructions will be provided.
19. 6 mL blood sample (red top tube) for serum and 20 mL blood sample (green top tubes) for peripheral blood mononuclear cell (PBMC) will be collected on Day 1 of Cycle 1 and 2, prior to dosing and at End of Treatment. Analyses may include (but are not limited to) examination of gpNMB expression (and/or potential binding partners for gpNMB) on myeloid suppressor cells; peripheral leukocytes; circulating tumor cells; and other immune response cells of interest (Section 11.2). Details on sample collection and handling will be provided.
20. 6 mL blood sample (red top tube) for Pharmacokinetic (PK) samples will be collected (Details on sample collection and handling will be provided.):
    - Phase I: Day 1 of Cycles 1 and 2, prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion) and 4-5 hours after the end of infusion. A PK sample will also be collected at Cycle 1, Days 8 and 15. Additional PK samples will be collected on Day 1 of Cycles 3 and 5 prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion) and at End of Treatment visit.
    - Phase II: Day 1 of Cycle 1, 2, and 5, prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion) and at End of Treatment visit.

21. Imaging-based evaluation per RECIST 1.1 should be performed. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as well as all other suspected disease sites is required. Magnetic resonance imaging (MRI) exams of the brain, abdomen, and pelvis can be performed in lieu of a CT; however MRI exams of the chest are not recommended. In the event that a chest MRI is performed, a non-contrast chest CT is strongly recommended to evaluate the lung parenchyma. Brain and/or bone scans are required for any patients with a history of metastases to bone and/or brain or where symptomatology raises the suspicion for bone and/or brain metastases. Lesions identified on bone scans should be confirmed by a CT or MRI at baseline, and, if identified as target lesions due to soft tissue component, they should continue to be followed by the same methodology (i.e., CT or MRI scan). However, bone lesions followed as non-target disease may be subsequently followed by bone scans only. Lesions that cannot be imaged but are assessable by clinical exam may be assessed by color photography including a ruler (preferred method) or measured with calipers. Normally, all target and non-target disease sites should be evaluated at each assessment. However, for patients with non-target bone disease, bone scans need only be repeated every twelve to eighteen weeks or more frequently if clinically indicated. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.
22. Unless otherwise specified, all study assessments should be performed prior to administration of study treatment, and may be performed up to 72 hours prior to treatment administration if assessments remain within the specified visit window.
23. All concomitant medication will be reviewed if taken within 28 days prior to Study Day 1, and either (whichever occurs sooner): a) 28 days after last dose of study treatment or b) initiation of alternate anti-cancer therapy. In addition, all concomitant medications taken to treat glembatumumab vedotin-related serious adverse events (SAEs) should be recorded in the electronic Case Report Form (eCRF) throughout the duration of the study/follow-up.
24. For patients who develop Grade 3 treatment-related rash and who provide appropriate consent, optional punch biopsies of the rash site and optional photographs of the rash site, as well as uninvolved skin, are strongly encouraged. Samples may be submitted for central analyses including quantification of gpNMB expression; in these cases, collection, processing and shipping instructions will be provided.
25. Events occurring >28 days after discontinuation of study treatment are only reportable if both serious (SAE) and potentially treatment-related.

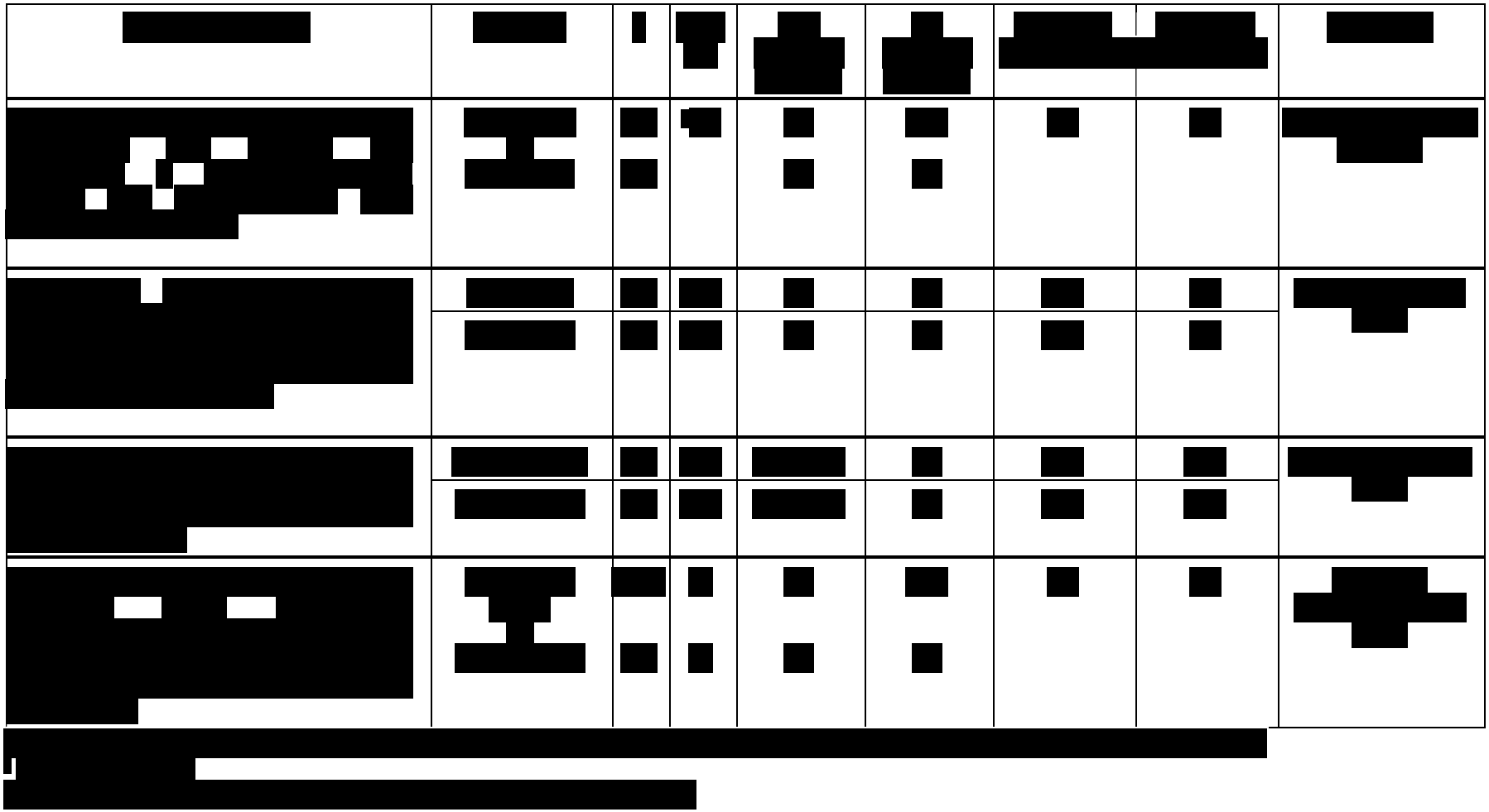
3. BACKGROUND/RATIONALE

3.1. Squamous Cell Lung Cancer



[redacted]

Table 2. NSCLC Clinical Trial Outcomes for Patients with Squamous Cell Histology



3.2. gpNMB

[redacted]

[redacted]

[redacted]

3.3. Glembatumumab Vedotin

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

Table 3. Study CR011-CLN-20: Activity Data in Patients with Advanced Breast Cancer

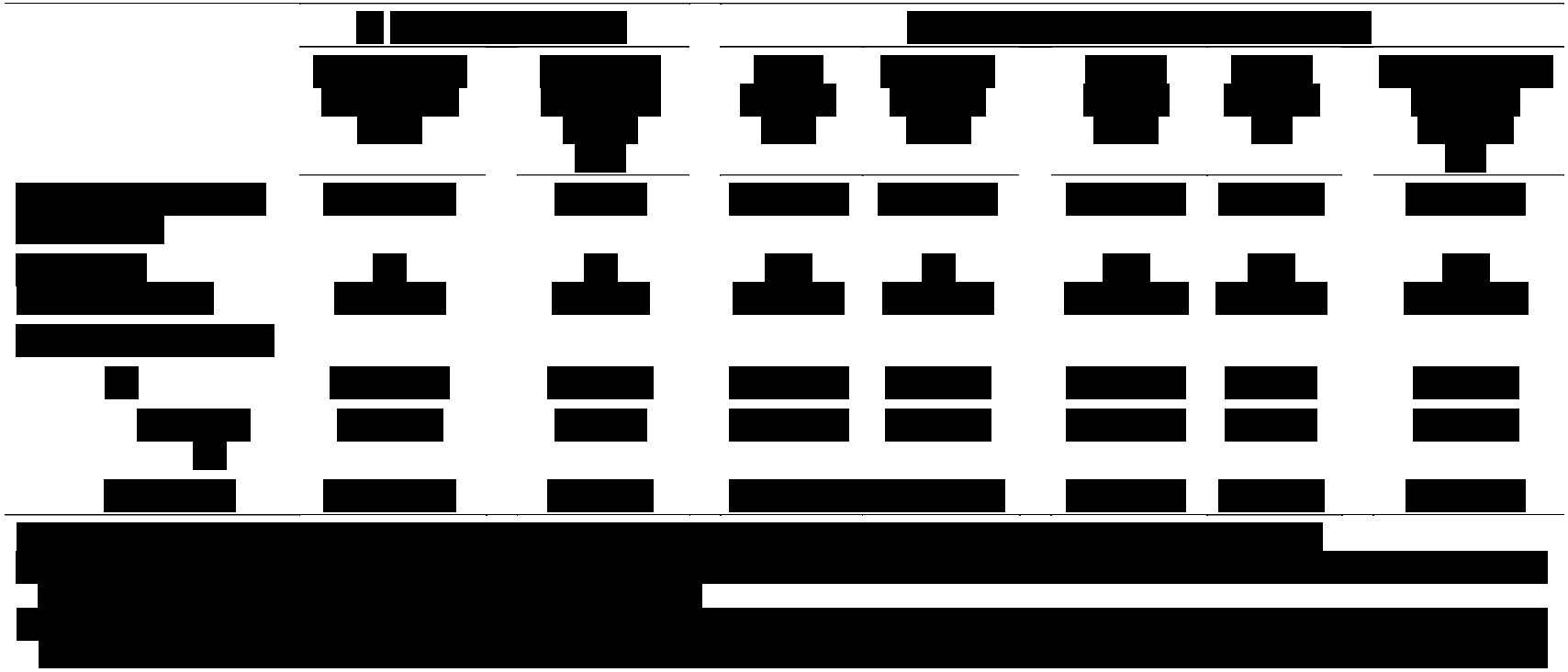


Table 4. Study CDX011-03 ("EMERGE"): Response Data for Patients with Advanced gpNMB-Expressing Breast Cancer

[redacted]

*

Figure 2. Study CDX011-03 ("EMERGE"): Progression-Free and Overall Survival for Patient Subgroups of Interest

Table 5. Study CR011-CLN-11: Activity Parameters by Dosing Schedule

[redacted]

Figure 3. Study CR011-CLN-11: Outcomes by gpNMB Expression Level

[redacted]

3.4. Study Rationale

[redacted]

4. STUDY OBJECTIVES

4.1. Primary Objective

Phase I

The primary objective of the Phase I portion of the study is to evaluate the safety and tolerability and to determine the Maximum Tolerated Dose (MTD) of glembatumumab vedotin in patients with advanced gpNMB-expressing SCC of the lung.

Phase II

The primary objective of the Phase II portion of the study is to determine the anti-tumor activity, as assessed by objective response rate (ORR) in accordance with RECIST 1.1, of the MTD of glembatumumab vedotin in patients with advanced gpNMB-expressing SCC of the lung.

4.2. Phase I & II Secondary Objectives

Secondary objectives are:

- To further characterize the safety of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung.
- To further evaluate the anti-cancer activity of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung, as measured by duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS).

4.3. Phase I & II Exploratory Objectives

Exploratory objectives are:

- To investigate if the anti-cancer activity of glembatumumab vedotin in advanced gpNMB-expressing SCC of the lung is dependent upon the degree of gpNMB expression in tumor tissue.
- To examine pharmacodynamic effects of treatment, including tumor immune cell infiltrate type and number; localization of glembatumumab vedotin, CR011 or Monomethylauristatin E (MMAE) at the tumor site; soluble mediators and/or gpNMB expression levels in tumor tissue; and analysis of peripheral blood cell subsets.
- To further characterize the pharmacokinetics and immunogenicity of glembatumumab vedotin in this patient population.

5. INVESTIGATIONAL PLAN

5.1. Overall Design and Plan of the Study

This is an open-label, single arm study of glembatumumab vedotin in patients with Stage IIIB or IV gpNMB-expressing SCC of the lung who have failed a prior platinum-based chemotherapy regimen. This study will include a dose-escalation phase followed by a 2-stage Phase II expansion, as follows:

Study Phase	Dose Level/ Cohort	Glembatumumab Vedotin Dose (mg/kg)	Patients (n)
Phase I Dose-Escalation	-1[2]	1.3	3
	1[1,3]	1.9	9 enrolled previously; to add 3-6 more
Phase II	Stage 1	MTD*	20
	Stage 2	MTD*	15

[1] Amendment 2: A maximum of three additional patients were treated on Dose Level/Cohort 1 (1.9 mg/kg) for 9 patients at this dose level to verify the safety of this dosage regimen (Section 5.1.1 for details).

[2] Three patients completed treatment on Dose Level/Cohort -1 with no DLTs.

[3] We will re-escalate to Dose Level/Cohort 1. An additional 3-6 patients will be treated on Dose Level 1 (up to 15 total).

* MTD as determined during the dose-escalation phase

All patients will be seen in the clinic at scheduled intervals during the treatment phase of the study. Patients will not be permitted to have concurrent chemotherapy, immunotherapy or other experimental therapies during study treatment.

Patients will receive glembatumumab vedotin in an open-label fashion, once every three weeks (q3w) by 90-minute intravenous (IV) infusion, until disease progression or intolerance. Tumor assessments will be performed every six (±1) weeks for six months, and every nine (±2) weeks thereafter, until progression. Tumor response will be assessed by the investigator in accordance with Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer, Therasse et al. 2009). Patients who discontinue treatment in the absence of progression, including those who discontinue treatment for adverse events, will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies.

5.1.1. Dose-Escalation Phase

For the dose-escalation phase, the starting dose of glembatumumab vedotin will be 1.9 mg/kg q3w (Cohort 1). This dose level is based upon the previously identified therapeutic dose of 1.88 mg/kg q3w, with rounding to 1.9 mg/kg for reasons of practicality and feasibility in preparation of the infusion. [redacted] Given the fact that one of the previously reported DLTs at 1.9 mg/kg in this study was complicated by the patient have progressive disease at the same time, and the other (pruritus) is a known and generally manageable adverse event associated with glembatumumab vedotin, it is reasonable to re-escalate, and re-explore the safety of the 1.9 mg/kg cohort.

Original Plan:

Initially, three patients will be enrolled to Cohort 1. In the event of 1 dose-limiting toxicity (DLT), the cohort will be expanded to 6 patients. In the event of ≥ 2 DLTs, the cohort will have exceeded the MTD, and the dose will de-escalate. In this case, 3 patients will be enrolled to Cohort -1 and the same DLT evaluation

rules will apply, such that 1 DLT will require expansion to 6 patients; this dose level will be deemed the MTD if DLT occur in 0/3 or ≤ 1/6 patients; and the study will cease if ≥ 2 DLTs occur at dose level -1.

Dose escalation from Cohort 1 to Cohort 2 may proceed if three patients in Cohort 1 complete the DLT observation period with 0 DLTs, or if six patients in Cohort 1 complete the DLT observation period with 0 or 1 DLTs. The MTD for the dose-escalation phase will be the highest dose-level where 0/3, or ≤ 1/6 patients in a cohort experienced a DLT.

Amendment 2.0:

As of February 14, 2017; six patients have been enrolled to dose level 1 (1.9 mg/kg) with reporting of one dose limiting toxicity (DLT). Two deaths have occurred on study. One patient had a Grade 5 respiratory failure deemed unrelated to study drug and likely related to disease under study by the site and Sponsor. A second patient also had a Grade 5 respiratory failure deemed as possibly related to study drug by the site as it could not be ruled out. This qualified as a DLT per protocol. Review of documents obtained from the site demonstrated the patient had serious medical conditions including a previous respiratory failure intensive care unit admission in August 2016. The patient's disease complicates the issue of assessing safety of the drug, and the events that transpired with this patient do not seem consistent with the drug toxicity profile of Glembatumumab Vedotin. The Sponsor assessed the respiratory failure as recurrent since the patient experienced respiratory failure previously in August 2016. It is the Sponsor's assessment that the DLT event for this patient is 'Grade 3 or higher neutropenia with associated fever greater than 38.1.' Out of the six patients whom were enrolled on dose level 1 (1.9 mg/kg), 1 DLT has been identified as noted above.

Dose escalation to Cohort 2 seemed premature. To further assess the safety signal and not put either subjects or the drug in jeopardy, it was PrECOG's decision to modify the Phase I portion and treat a maximum of 3 additional patients on Cohort 1 (1.9 mg/kg) for up to 9 patients at this dose level to verify the safety of this dosage regimen. If any of the 3 additional patients experience a DLT, the dose will de-escalate to Cohort -1. If none of the additional 3 patients experience a DLT, dose escalation may proceed form Cohort 1 to Cohort 2. The same DLT evaluation rules will apply as noted above.

A second DLT was observed on Cohort 1. Patient experienced treatment- related Grade 3 pruritus requiring hospital admission. Although a vital organ was not involved, due to the extent and intensity of the treatment required for pruritus, it was considered a DLT. Dose was de-escalated to Dose Level -1.

Amendment 3.0:

Three patients were enrolled to Dose Level -1 with no DLTs during the 42 day assessment period.

Given the fact one of the previously reported DLTs at 1.9 mg/kg was complicated by the patient have progressive disease at the same time, and the other (pruritus) is a known and generally manageable adverse event associated with glembatumumab vedotin, it is reasonable to re-escalate, and re-explore the safety of the 1.9 mg/kg cohort.

The protocol is being amended to include a plan to re-escalate to Dose Level 1. Upon re-escalation to Dose Level 1, 3 patients will be treated. This dose level will be deemed unsafe if at least 2 patients among the first 3 patients enrolled experiences a DLT, and Dose Level -1 will be deemed the MTD. If no DLTs are observed among the first 3 patients or if 1/3 patients experiences a DLT then we will enroll 3 more patients. This dose level will be determined to be the MTD in the event that <2/6 patients treated at Dose Level 1 experience DLT. If ≥ 2/6 patients experience DLT at Level 1, then Dose Level -1 will be declared the MTD. Note that Dose Level 2 is no longer part of the study effective with this amendment.

The DLT evaluation period for determination of the appropriateness of dose-escalation will be through the end of the second treatment cycle (Section 6.1.7). Patients who discontinue safety follow-up before day 42 (±3 days) for reasons other than DLT will be replaced (Section 6.1.7 for DLT definition).

Any DLT at any time point during the study must be reported to PrECOG (or designee) as soon as possible, but no later than 24 hours following the site becoming aware of the event, and PrECOG will distribute such notification to all participating sites within 24 hours of notification. Site teleconferences between PrECOG

and all participating sites will be held at frequent intervals and prior to dose-escalation to each cohort during the dose-escalation phase. PrECOG study personnel, including but not limited to the Study Chair(s), statistician, medical monitor and participating investigators, as applicable, will review toxicities from the current cohort during the site teleconferences before initiating enrollment into the next planned dose cohort.

5.1.2. Phase II Phase

Following determination of the MTD, a Phase II study portion will enroll up to 35 eligible, treated patients to further assess the safety and efficacy of glembatumumab vedotin. Patients who discontinue study for reasons other than symptomatic deterioration or death prior to the first radiographic assessment will be considered unevaluable and will be replaced.

Enrollment to the Phase II study portion will proceed according to a two-stage trial design (Simon 1989), so that enrollment may terminate early if the results are not sufficiently promising to warrant further study. In Stage 1, approximately 20 eligible, treated patients will be enrolled. If ≥ 2 patients achieve a tumor response (Partial Response [PR] or Complete Response [CR]); an additional 15 eligible, treated patients will be enrolled in Stage 2, for a maximum total of 35 eligible, treated patients. To assure sufficient eligible, treated patients, up to 2 additional patients may be enrolled.

Additionally, we will monitor for the incidence of Grade 5 events. In particular, we will monitor the Grade 5 event rate among the first stage accrual of 20 patients. All Grade 5 events deemed at least possibly related to treatment as well as any Grade 5 events occurring within 3 weeks of the first dose (Cycle 1) regardless of attribution are included as 'events' for the purpose of monitoring. See Section 10.2.2.1 for details.

5.2. Selection of Study Population

Each of the inclusion and exclusion criteria must be met in order for a patient to be considered eligible for this study. An eligibility checklist is provided in Appendix 1 to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

***Phase I Only: Eligibility Criteria Checklist must be sent via fax (215-557-7169) or email (candrews@precogllc.org) to the PrECOG PM/designee for review and approval prior to subject registration. Site will receive a confirmation of approval. Once confirmation of approval is received subject can be registered.**

PrECOG will not grant any exceptions or waivers to protocol eligibility criteria.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

NOTE: All questions regarding eligibility should be directed to the PrECOG Project Manager. Questions will be further discussed with the medical leads for the trial as deemed appropriate (e.g., medical monitor, study chair).

5.2.1. Number of Patients

Approximately 55 patients will be enrolled. Enrollment will be on a first-come basis, with no pre-defined maximum enrollment per clinical site.

5.2.2. Subject Eligibility

5.2.2.1. Inclusion Criteria

1. Read, understood, and provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.
2. Male or female patients with metastatic, histologically- or cytologically-confirmed Stage IIIB or IV non-small cell lung cancer (NSCLC) of squamous histology (Staging per American Joint Committee on Cancer [AJCC], Edition 7). Mixed histology adenosquamous NSCLC will also be permitted.

3. Experienced progression/recurrence of disease during or subsequent to the most recent anti-cancer regimen.
4. Any number of prior lines of systemic therapy may have been received for advanced (recurrent, locally advanced, or metastatic) SCC of the lung, but at least one must have been a platinum-based chemotherapy regimen. Platinum therapy may be given on-label or as part of a clinical trial.
5. Lung cancer confirmed to express gpNMB, as assessed by immunohistochemistry at a central lab (using expression in ≥ 5% of tumor epithelial cells as a cut-off for positivity). This can be tested on archived tissue if available, although preferred tumor specimen is a biopsy after the most recent therapy.

   NOTE: Additional samples from previous collection dates should also be submitted when feasible. Submitted cytology samples such as pleural effusions, bronchial washings or fine needle aspirates (FNA) will be used to evaluate feasibility of gpNMB expression analysis and to investigate correlations with other samples for the patient, but they will not be used for determination of study eligibility. For patients with multiple samples submitted, eligibility will be based on the most recently obtained sample, or, if obtained on the same date, the sample with the highest level of gpNMB expression. However, in the event that disparate results are obtained for samples received within a similar timeframe (i.e., within a 6-month period), the medical monitor may be consulted for determination of eligibility.
6. Age ≥ 18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (Appendix 2).
8. Measurable disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) [Appendix 3]. Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.
9. Resolution of all toxicities related to prior therapies to ≤ NCI-CTCAE Grade 1 severity or back to baseline, except for alopecia, vitiligo, or endocrinopathies on replacement therapy.
10. Adequate bone marrow function as assessed by absolute neutrophil count (ANC) ≥ 1500/mm^3; hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm^3.
11. Adequate renal function as assessed by serum creatinine ≤ 2.0 mg/dL; or calculated (Cockcroft and Gault Formula; Appendix 4) or 24-hour urine creatinine clearance >40 mL/min.
12. Serum albumin≥ 3 g/dL.
13. Adequate liver function as assessed by total bilirubin ≤ 1.5x upper limit of normal (ULN), and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5x ULN (≤ 5.0x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.

    NOTE: The liver is a route of clearance for MMAE. Patients with mild hepatic impairment are excluded from Phase I (the dose escalation portion) to minimize the influence of hepatic impairment on tolerability and dose selection because a lower dose is recommended for other ADCs with a vc-MMAE moiety. **See the acceptable liver function parameters for Phase I defined above.** In Phase II (the dose expansion portion), a lower starting dose for patients with mild hepatic impairment will be determined based on the MTD recommended from the Phase I portion of this trial. **The acceptable liver function parameters will be redefined for Phase II.**
14. Both male and female patients of childbearing potential enrolled in this trial must use adequate birth control measures during the course of the trial and for at least one month after discontinuing study drug. Adequate birth control measures are defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, or intrauterine device), implants, injectables, combined oral contraceptives, sexual abstinence (abstinence from intercourse during the ovulation period), or vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.
15. Willing to provide blood samples for research purposes (Section 11.2).

5.2.2.2. Exclusion Criteria

1. Received glembatumumab vedotin (CR011-vcMMAE; CDX-011) or other MMAE-containing agents previously.

2. Chemotherapy within 21 days or at least 5 half-lives (whichever is shorter) prior to the planned start of study treatment; radiation outside the thorax within 14 days prior to the planned start of study treatment or thoracic radiation; antibody based therapy or investigational therapy within 28 days prior to the planned start of study treatment.
3. Neuropathy >NCI-CTCAE Grade 1.
4. Subjects with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin. Compounds of similar composition include Auristatin PHE as an anti-fungal agent, Auristatin PE (TZT-1027, Soblidotin, NSC-654663) as an anti-tumor agent and Symplostatin 1 as an anti-tumor agent.
5. Known brain metastases, unless previously treated and patients are neurologically returned to baseline except for residual signs and symptoms related to Central Nervous System (CNS) treatment and CNS lesions are not progressive in size and number for 4 weeks.
6. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, and congestive heart failure (New York Heart Association (NYHA) Class 3 or 4 [Appendix 5]) related to primary cardiac disease, a history of a serious uncontrollable arrhythmia despite treatment, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry.
7. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary.

   NOTE: Microscopic examination of urinalysis is required during screening. If urinary infection is suspected, a negative urine culture is required prior to enrollment.
8. Subjects on immunosuppressive medications such as azathioprine, mycophenolate mofetil, cyclosporine or require chronic corticosteroid use (defined as ≥ 3 months of prednisone dose equivalent of ≥ 10 mg).
9. The MMAE component of glembatumumab vedotin is primarily metabolized by CYP3A. Patients taking strong CYP3A inhibitors and inducers are excluded in Phase I (the dose escalation portion) to minimize the effect of these modulators on exposure, tolerability and dose selection (http://medicine.iupui.edu/clinpharm/ddis/main-table/).
10. History of other malignancy except for adequately treated basal or squamous cell skin cancer, curatively treated in situ disease, or any other cancer from which the patient has been disease-free for ≥ 2 years.
11. Pregnant or breast-feeding women.
12. Subjects must not be on home oxygen therapy (intermittent or continuous).
13. Any underlying medical condition that, in the Investigator's opinion, will make the administration of study treatment hazardous to the patient, or would obscure the interpretation of adverse events.

5.2.3. Regulatory Requirements

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Required documents will be reviewed, and approved by PrECOG or their representative. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients will begin protocol therapy without formal registration as per the process below.

5.2.4. Patient Registration

Phase I Registration: Prior to discussing protocol entry with the patient **AND** prior to registering in the electronic data capture (eDC) system, call the assigned PrECOG Project Manager to ensure that a place on the protocol is open to the patient.

***Phase I Only: Eligibility Criteria Checklist must be sent via fax (215-557-7169) or email (candrews@precogllc.org) to the PrECOG PM/designee for review and approval prior to subject registration. Site will receive a confirmation of approval. Once confirmation of approval is received subject can be registered.**

The Phase II portion will be conducted using the dose and schedule selected from the Phase I portion of the study. Patients that participate in Phase I will not be eligible to participate in Phase II.

Phase II Registration: Prior approval of patient registration is not required.

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 5.2.2.1 and 5.2.2.2 prior to registration. Treatment should begin ≤ 10 working days from study entry (date of registration).

An eligibility checklist is included in Appendix 1 and the Study Reference Manual (SRM). A confirmation of eligibility assessment by the investigator and/or site will be performed during the registration process.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via the eDC system. Confirmation of registration will be displayed in the eDC system once the site personnel have verified the subject's eligibility status.

Full information regarding registration procedures and guidelines can be found in the SRM provided to sites. All correspondence regarding patient registration must be kept in the study records.

5.2.5. Measures to Minimize Bias

This is non-randomized open-label study. The analysis of tumor response and PFS will be based on tumor response assessments performed by the investigator according to standardized, objective response criteria (RECIST 1.1). In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an Independent Review Committee (IRC), blinded to investigator assessments.

5.2.6. Withdrawals and Replacement of Patients

Every effort should be made within the bounds of safety and patient choice to have each patient complete the study. An explanation will be recorded for each patient taken off study treatment or discontinuing the study.

In the dose-escalation phase, patients who discontinue safety follow-up before day 42 (±3 days) for reasons other than DLT will be considered unevaluable for DLT assessment and will be replaced.

5.2.6.1. Discontinuation of Study Treatment

Reasons for discontinuation of study treatment include:

1. Progressive disease, as assessed by the treating investigator in accordance with RECIST 1.1 criteria (Appendix 3);
2. Symptomatic deterioration (clinical progression);
    - Note: This category is applicable to patients with a global deterioration of health status requiring discontinuation of treatment. However, per RECIST 1.1 (Appendix 3), symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. Thus, every effort should be made to continue disease assessments per protocol until documented objective progression or initiation of alternate therapy.
3. Receipt of alternate anti-cancer treatments;
    - Note: Patients who undergo surgical resection or radiation in the absence of progression will have glembatumumab vedotin temporarily withheld during treatment and for at least 21 days after completion of surgical resection or radiation treatment or until patient has recovered from any adverse events resulting from the surgical or radiation intervention before restarting treatment with

glembatumumab vedotin. Patients may remain on the study and continue to receive study treatment until remaining lesions meet criteria for progression of disease.

4. Intercurrent illness that prevents further administration of treatment per investigator discretion;
5. Withdrawal request by the patient or the patient's legal representative;
   - Note: Withdrawal of consent for continued treatment should be differentiated from withdrawal of consent for study follow-up, and every effort should be made within the bounds of safety and patient choice to have each patient complete the study follow-up.
6. Unacceptable adverse event, including the development of DLT (Section 6.1.7);
7. Physician Decision;
8. Non-compliance of the patient;
9. Pregnancy;
10. Death, otherwise not explainable by the above options;
11. Patient lost to follow-up. (see below).

Patients who discontinue glembatumumab vedotin should be seen for an End of Treatment Visit. Patients who discontinue treatment in the absence of progression, including for adverse events, will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies **(Table 1)**.

5.2.6.2. Discontinuation from Study

Reasons for patient removal from the study include:

1. Request of the patient or the patient's legal representative (withdrawal of consent for the study follow-up);
2. Patient lost to follow-up. A subject should be considered lost to follow up only after multiple efforts have been made to contact the subject to assess his/her health status after failure of the subject to attend scheduled visits. If after 2 documented phone calls the investigative site is still unable to contact the subject, a certified letter should be sent to his/her home for immediate response. If there is still no response, the subject is to be considered lost to follow up. A record of the subject being lost to follow up should be noted in the source documents along with the phone contacts and the returned certified mail (if sent back).

5.2.7. Completion of Study

It is anticipated that the enrollment period will be approximately 30 months (Phase I: 12 months and Phase II: 18 months). All patients will be followed with regard to survival until death, discontinuation from study follow-up, or termination/completion of study. Patients who die or complete the study follow-up through study closure will be considered to have "completed" the study. The study will be declared complete when sufficient data is obtained to conclude the study; this is estimated at 15 months from the date when the last patient in the study discontinues study treatment.

Premature termination of this study may occur because of a regulatory authority decision, drug safety issues, or at the discretion of PrECOG. In addition, Celldex Therapeutics, Inc., the manufacturer of the study drug, retains the right to discontinue development of glembatumumab vedotin at any time.

6. STUDY TREATMENT

6.1. Glembatumumab Vedotin

6.1.1. Description, Packaging and Labeling

[redacted]

6.1.2. Accountability

[redacted]

6.1.3. Compliance

[redacted]

6.1.4. Storage

[redacted]

6.1.5. Preparation and Administration

[redacted]

6.1.5.1. Administration

[redacted]

6.1.6. Dose Modifications

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

6.1.7. DLT definition

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.1.8. Potential Toxicity and Management of Toxicity

6.1.8.1. Previously Observed Toxicities

[redacted]

6.1.8.2. Management of Toxicity

[redacted]

[redacted]

[redacted]

6.1.9. Additional Warnings and Precautions

6.1.9.1. Toxicity Associated with Similar Products

[redacted]

6.1.9.2. Drug-Drug Interactions

[redacted]

[redacted]

6.1.9.3. Hypersensitivity, Infusion Reaction

[redacted]

6.1.9.4. Infusion Site Extravasation

[redacted]

6.1.9.5. Antagonism of gpNMB

[redacted]

6.1.9.6. Exposure to Free MMAE

[redacted]

6.1.9.7. Renal Impairment

[redacted]

6.1.9.8. Hepatic Impairment

[redacted]

[redacted]

6.1.9.9. Pregnancy

[redacted]

7. CONCOMITANT THERAPY

While on study, when clinically appropriate, patients should strictly follow the study-prescribed treatment regimen. Therefore, patients should not receive additional investigational agents or anti-cancer therapies, unless recurrence/progression of disease warrants discontinuation of study treatment and commencement of alternate therapies.

The effect of glembatumumab vedotin on the absorption, metabolism, or excretion of other drugs has not been studied. Drugs known to strongly inhibit CYP3A4 should be used with caution, and drugs known to be potent CYP3A4 inducers should be avoided, if at all possible, while patients are exposed to glembatumumab vedotin (Section 6.1.9.2). A table listing P450 enzyme-drug interactions is available at: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Subjects may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. During study treatment, patients may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management. Anti-emetics and steroids for chemotherapy premedication are also permitted. Efforts should be made to maintain stable doses of concomitant medications during the course of treatment with glembatumumab vedotin.

Prolonged use of systemic corticosteroids above the physiologic dose (5 mg prednisone or equivalent) should be avoided, if possible, during the study do to a potential increase in risk of infections. Patients who receive prolonged or high dose steroids should be monitored closely for signs of infection.

If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously non-resectable tumor), these interventions are permitted, but should be avoided if clinically feasible until after the 12 week response assessment. A tumor response assessment should be conducted prior to any intervention, in order to document progression and/or confirm an objective response. Patients who undergo surgical resection or radiation in the absence of progression will have glembatumumab vedotin temporarily withheld during treatment and for at least 21 days after completion of surgical resection or radiation treatment or until patient has recovered from any adverse events resulting from the surgical or radiation intervention before restarting treatment with glembatumumab vedotin. Patients may continue to receive study treatment until remaining lesions meet criteria for progression of disease.

All concomitant medication will be reviewed if taken within 28 days prior to Study Day 1, and either (whichever occurs sooner): a) 28 days after last dose of study treatment; or b) initiation of alternate anti-cancer therapy. In addition, all anti-cancer medications and concomitant medications taken to treat glembatumumab vedotin-related SAEs should be recorded in the eCRF throughout the duration of study/follow-up.

8. STUDY PROCEDURES

8.1. Schedule of Investigations and Data Collection

The study is divided into phases with associated evaluations and procedures that must be performed at specific time points, as described in the following sections. The Schedule of Assessments **(Table 1)** summarizes the frequency and timing of various activity, safety, and other measurements.

8.1.1. Screening Period

Prior to the performance of any study-specific procedures, the patient will have the nature of the study explained to them, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained prior to any study-specific procedures that do not form a part of the patient's normal care. However, assessments performed according to standard of care prior to receipt of informed consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.

The assessments outlined for the Screening Visit in the Schedule of Assessments **(Table 1)** will be completed for each patient prior to inclusion in the study, and results will be evaluated to verify entry criteria prior to study treatment assignment.

8.1.2. Study Enrollment/Treatment Assignment

Patients who are screened and do not meet all entry criteria will not be entered in the clinical database. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued patients will not be re-used.

Enrollment should occur only after confirming all inclusion criteria and none of the exclusion criteria have been met.

For patients who are registered but do not receive any protocol therapy, baseline and follow-up information per Schedule of Assessments **(Table 1)** will be collected.

8.1.3. Treatment Phase

Specific procedures to be performed at each visit during the treatment phase are illustrated in the Schedule of Assessments **(Table 1)**. The End of Treatment Visit should be performed within 28 days after last study drug dosing and prior to initiation of alternate therapies. As described in Section 8.2.2.3, any abnormalities (adverse events) attributed to study drug dosing, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

8.1.4. Disease Assessment Visits

Disease assessments will be performed every 6 (±1) weeks for 6 months and every 9 (±2) weeks thereafter, until documented progression of disease or initiation of alternate anticancer therapies. Patients who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies.

8.1.5. Survival Follow-Up

Subsequent to progression of disease, all patients will be followed at 12 (±2) week intervals until study closure, as described in **Table 1, Footnote 7.**

8.2. Methods of Assessment

8.2.1. Activity

8.2.1.1. Anti-Tumor Activity

Anti-tumor activity will be assessed via ORR, DOR, PFS, and OS. Tumor response and progression will be defined by the investigator, according to RECIST 1.1 criteria. In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an IRC, blinded to investigator assessments.

8.2.1.2. Immunogenicity

Patients will be monitored for the development of anti-glembatumumab vedotin and anti-CR011 antibodies, and whether these antibodies are neutralizing.

8.2.1.3. Pharmacokinetic Evaluations

Concentration of the antibody-drug conjugate (ADC), total antibody (TA) and free MMAE will be determined using Good Laboratory Practices (GLP) compliant enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The impact of circulating gpNMB levels on pharmacokinetic parameters may also be examined.

8.2.1.4. Pharmacodynamics

Pharmacodynamic parameters will be evaluated via assessment of post-treatment tumor tissue obtained via voluntary biopsy or resection and/or blood samples. Parameters evaluated may include localization of glembatumumab vedotin, CR011 or MMAE at the tumor site and/or gpNMB levels on cells in blood and tumor tissue, as well as evaluation of tumor infiltrating and peripheral leukocytes, circulating tumor cells and other immune response cells of interest. Soluble gpNMB levels in circulation may also be examined.

8.2.2. Safety Variables

8.2.2.1. Adverse Events (AEs): Definition

An adverse event is any untoward medical occurrence in a patient administered a study treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. All observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be reported as described in the following sections. For the purposes of this current study, “study treatment” is defined as glembatumumab vedotin.

After informed consent, but prior to initiation of study treatment (glembatumumab vedotin), only AEs/SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). After the initiation of study treatment, all identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF).

For all adverse events, the investigator is responsible for obtaining information adequate to determine:

– Appropriate descriptive term: Adverse events should be reported using concise medical terminology, preferably referring to the syndrome/diagnosis rather than symptoms, when possible.

– Severity: Adverse event severity will be primarily assessed using NCI Common Terminology Criteria for Adverse Events V4.0. (NCI-CTCAE), Version 4.0, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institute of Health (NIH), Department of Health and Human Services (DHHS):

  http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

- Onset/resolution dates and outcome
- Causality: The relationship of each adverse event to study drug will be defined as "unrelated" or "related" to study treatment:
    - Unrelated: There is little or no possibility that the study drug caused the reported adverse event; and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications appear to explain the adverse event.
    - Related: There exists at least a reasonable possibility that the study treatments caused or contributed to the adverse event; an inability to identify an alternate etiology for an adverse event should not, by itself, justify a "related" attribution.
- whether it meets the criteria for classification as a serious adverse event (Section 8.2.2.2)

The following study-specific points of clarification should be noted when considering AE reporting and recording:

- Progression of neoplasia should not be reported as an AE or SAE. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an AE, and hospitalizations due to the progression of cancer do not necessarily qualify for a SAE. If there is any uncertainty about a finding or event being due solely to progression of neoplasia, the finding or event should be reported as an AE or SAE as appropriate. Death due to disease progression occurring within 28 days of study treatment should be reported to PrECOG within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a SAE.
- Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response, and recorded. For example, if an AE due to recurrence/progression of disease necessitates discontinuation from the study, the primary reason for study discontinuation should be recorded as "Recurrence/Progression of Disease" (not AE).
- Abnormal objective test findings should be reported as AEs if the findings are associated with accompanying symptoms, require additional diagnostic testing or medical/surgical intervention, lead to dose modification/discontinuation of study treatment and/or are considered otherwise clinically significant.
- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.
- Any AEs/SAEs resulting in death should be recorded with an end date equal to the death date, while other events ongoing at the time of death should be recorded with an outcome of "continuing". If requested, a summary of available autopsy findings should be submitted as soon as possible to PrECOG.

8.2.2.2. Serious Adverse Events (SAEs): Definition

An SAE is any adverse event from this study that results in one of the following outcomes:

- Death (any AE that has a fatal outcome must be assigned NCI-CTCAE Grade 5)
- Requires initial or prolonged inpatient hospitalization (This criterion would exclude hospitalization in the absence of a precipitating AE, such as admission for treatment of a preexisting condition not associated with a new/worsening AE, or admission for elective surgery. As well, admission to rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries are not considered "hospitalizations" for the purpose of this criterion.)

- Is life-threatening (defined as an event in which the study patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Is a persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other significant medical hazard (Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

The following study-specific points of clarification should be noted when considering SAE reporting and recording:

- Progression of neoplasia should not be reported as an AE or SAE. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an AE, and hospitalizations due to the progression of cancer do not necessarily qualify for a SAE. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an AE or SAE as appropriate. Death due to disease progression occurring within 28 days of study treatment should be reported to PrECOG within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a SAE.
- The following, although not necessarily meeting criteria for an SAE, should also be reported to PrECOG according to SAE reporting processes:
    - New primary cancers that occur during protocol treatment or protocol-mandated follow-up must be reported within 30 days of diagnosis, regardless of relationship to protocol treatment. A copy of the pathology report, if applicable, should be sent, if available.
    - If a female becomes, or is found to be, pregnant within 6 months of exposure to the study treatments (maternal exposure) or if a male has been exposed to the study treatments within 6 months prior to conception (paternal exposure).
    - Any follow-up to the above-referenced events, including outcome of pregnancy. Further follow-up of birth outcomes will be handled on a case-by-case basis. In the case of paternal exposure, the investigator must obtain permission from the subject's partner in order to conduct any follow-up or collect any information.

8.2.2.3. AE/SAE Reporting

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

AEs and SAEs should be recorded from the time the subject has taken at least one dose of study treatment through (whichever occurs first) either a) 28 calendar days after the last administration of study treatment, or b) initiation of alternate anticancer therapy.

However:

- Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study treatment is suspected.
- For AEs or SAEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve to ≤ Grade 1, or stabilize for at least three months after the last administration of study treatment (whichever is sooner).

All AEs will be reported. All SAEs will also be reported in an expedited fashion using the Serious Adverse Event Report. The AEs entered in the eCRF and SAE Reports must be completed in a consistent manner; for example, the same adverse event term, causality, severity, and onset/resolution dates should be used on both forms.

The investigator should inform PrECOG of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on the PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. A copy of the fax transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records.

All SAEs should be faxed to 888-731-8999 or scanned and emailed to pre0504@qdservices.com as per the instructions found in study materials provided to the investigator site.

[redacted]	Manager, Clinical Safety
Medical Monitor	During normal business hours
During normal business hours	(8:30 am-5:00 pm EST):
(8:30 am-5:00 pm EST):	Phone: 610-354-0404
Phone: 610-354-0404	After normal business hours:
After normal business hours:	Cell: 484-574-2367
Phone: 484-574-2367	
[redacted]	

PrECOG will notify Celldex Therapeutics, Inc. of all SAE's within 24 hours of PrECOG's Awareness Date as discussed above. Relevant follow-up information will be provided to Celldex Therapeutics, Inc. as soon as it becomes available.

Investigators should also report event(s) to their Institutional Review Board (IRB) as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

All SAEs, regardless of causality, must be collected which occur within 28 days of last dose of study treatment. This includes all deaths within 28 days of last dose of glembatumumab vedotin regardless of attribution. In addition, the Investigator should notify PrECOG or designee of any SAE that may occur after this time period which they believe to be definitely, probably or possibly related to investigational product.

Serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by PrECOG (or designee) in accordance with 21CFR312.32 and international regulations, as appropriate.

8.2.2.4. Laboratory Safety Data

The following clinical laboratory tests will be performed during this study to assess safety (Schedule of Assessments **Table 1** for specific tests):

- Hematology
- Serum Chemistries
- Urinalysis

Investigators must document their review of each laboratory report by signing or initialing and dating each report, as well as addressing the clinical significance and causality (for significant abnormalities). Section 8.2.2.1 provides further guidance as to when abnormal laboratory results are to be reported as adverse events.

8.2.2.5. Other Safety Data

The following evaluations will also be performed during the study to measure the safety and tolerability of glembatumumab vedotin:

- Vital sign measurements
- Physical examination
- ECGs
- ECOG performance status (Appendix 2)

9. DATA SAFETY MONITORING BOARD (DSMB)

The PrECOG data safety monitoring board (DSMB) will review cumulative data on an interim basis. The interim data reviews may include but are not limited to objectives and summaries of adverse events. The DSMB will conduct reviews approximately every 6 months, or as frequently as deemed necessary by the DSMB. If a safety concern is identified, the DSMB may recommend halting or permanently stopping the trial at any time.

10. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by PrECOG.

This documentation may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

10.1. Analysis Endpoints

Primary

- Phase I: Safety and determination of the MTD
- Phase II: Objective response rate (ORR)

Secondary

- Duration of objective response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

Correlative:

- Concentration of ADC, TA and free MMAE
- Pharmacodynamic parameters, including gpNMB expression levels in serum and tumor tissue; localization of glembatumumab vedotin, CR011 or MMAE at the tumor site; evaluation of tumor infiltrating and peripheral leukocytes, circulating tumor cells and other immune response cells of interest; and circulating soluble gpNMB.

Safety

- Incidence of adverse events
- Deaths on study
- Discontinuations of study drug due to adverse events
- Changes in hematology, chemistry, and other laboratory parameters
- Changes in vital sign parameters
- Changes in ECGs parameters

10.2. Sample Size and Power Calculation

10.2.1. Phase I Escalation Phase

Original Plan:

Three to 6 patients will be enrolled in each dose cohort based on a standard Phase I dose escalation scheme (Dose Level 1 will enroll up to 9 patients as noted in Section 5.1.1). Each patient will participate in only 1 dose cohort. The total number of patients to be enrolled in the dose escalation phase is dependent upon the observed safety profile after 2 cycles, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD up to the second dose cohort of 2.2 mg/kg.

A starting sample size of 3 patients per dose cohort, expanding to 6 patients in the event of a marginal DLT rate (33%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be

halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 83% chance that dose escalation would be halted in a given cohort.

Amendment 2.0:

As of February 14, 2017; six patients have been enrolled to dose level 1 (1.9 mg/kg) with reporting of one dose limiting toxicity (DLT). Two deaths have occurred on study. One patient had a Grade 5 respiratory failure deemed unrelated to study drug and likely related to disease under study by the site and Sponsor. A second patient also had a Grade 5 respiratory failure deemed as possibly related to study drug by the site as it could not be ruled out. This qualified as a DLT per protocol. Review of documents obtained from the site demonstrated the patient had serious medical conditions including a previous respiratory failure intensive care unit admission in August 2016. The patient's disease complicates the issue of assessing safety of the drug, and the events that transpired with this patient do not seem consistent with the drug toxicity profile of Glembatumumab Vedotin. The Sponsor assessed the respiratory failure as recurrent since the patient experienced respiratory failure previously in August 2016. It is the Sponsor's assessment that the DLT event for this patient is 'Grade 3 or higher neutropenia with associated fever greater than 38.1.' Out of the six patients whom were enrolled on dose level 1 (1.9 mg/kg), 1 DLT has been identified as noted above.

Dose escalation to Cohort 2 seemed premature. To further assess the safety signal and not put either subjects or the drug in jeopardy, it was PrECOG's decision to modify the Phase I portion and treat a maximum of 3 additional patients on Cohort 1 (1.9 mg/kg) for up to 9 patients at this dose level to verify the safety of this dosage regimen. If any of the 3 additional patients experience a DLT, the dose will de-escalate to Cohort -1. If none of the additional 3 patients experience a DLT, dose escalation may proceed form Cohort 1 to Cohort 2. The same DLT evaluation rules will apply as noted above.

A second DLT was observed on Cohort 1. Patient experienced treatment- related Grade 3 pruritus requiring hospital admission. Although a vital organ was not involved, due to the extent and intensity of the treatment required for pruritus, it was considered a DLT. Dose was de-escalated to Dose Level -1.

Amendment 3.0:

Three patients were enrolled to Dose Level -1 with no DLTs during the 42 day assessment period.

Given the fact one of the previously reported DLTs at 1.9 mg/kg was complicated by the patient have progressive disease at the same time, and the other (pruritus) is a known and generally manageable adverse event associated with glembatumumab vedotin, it is reasonable to re-escalate, and re-explore the safety of the 1.9 mg/kg cohort.

The protocol is being amended to include a plan to re-escalate to Dose Level 1. Upon re-escalation to Dose Level 1, 3 patients will be treated. This dose level will be deemed unsafe if at least 2 patients among the first 3 patients enrolled experiences a DLT, and Dose Level -1 will be deemed the MTD. If no DLTs are observed among the first 3 patients or if 1/3 patients experiences a DLT then we will enroll 3 more patients. This dose level will be determined to be the MTD in the event that <2/6 patients treated at Dose Level 1 experience DLT. If ≥ 2/6 patients experience DLT at Level 1, then Dose Level -1 will be declared the MTD. Note that Dose Level 2 is no longer part of the study effective with this amendment.

10.2.2. Phase II Study Portion

In the Phase II study portion, the safety and preliminary antitumor activity of glembatumumab vedotin at the selected dose will be explored. Up to 35 eligible, treated patients may be enrolled according to a single-arm Phase II trial design with ORR as the primary endpoint.

The Phase II study portion will be carried out in 2 stages so that enrollment can terminate early in the event that glembatumumab vedotin is not sufficiently active in this patient population. A true ORR of 20% is hypothesized. A response rate of less than 5% is not considered clinically meaningful. The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on Simon's 2-stage design, with 90% power and 1-sided significance level of less than 10%. Based on the above considerations, 20 eligible, treated patients will be enrolled (first

stage): if ≤1 patient achieves a complete response (CR) or partial response (PR), then enrollment will terminate; otherwise, 15 additional eligible, treated patients will be enrolled in the second stage, for a total of 35 eligible, treated patients. To assure sufficient eligible, treated patients, up to 2 additional patients may be enrolled (total of 37 patients).

Upon completion of the second stage, if ≥ 4 patients out of the 35 eligible, treated patients achieve confirmed CR or PR, then the true response rate for glembatumumab vedotin likely exceeds 5%, the lower threshold of a clinically meaningful response rate. Alternatively, if <4 patients achieve an objective response at the end of the second stage, then the true response rate is likely 5% or lower and further evaluation of glembatumumab vedotin in this patient population may not be pursued. If the true ORR is less than 5%, the probability of terminating enrollment at the end of the first stage is equal to 74%.

Safety will be assessed for all patients enrolled in an ongoing fashion based on the incidence of AEs, SAEs, and treatment discontinuations due to AE. No formal safety stopping rules are specified. However, if any significant safety issues arise, a decision to modify or terminate the trial will be made.

An interim analysis will be performed for the Phase II study portion to determine if enrollment in the second stage will commence based on the criteria described in Section 10.2.

10.2.2.1. Toxicity Monitoring

This study will be monitored for the incidence of Grade 5 events. In particular, we will monitor the Grade 5 event rate among the first stage accrual of 20 patients. All Grade 5 events deemed at least possibly related to treatment as well as any Grade 5 events occurring within 3 weeks of the first dose (Cycle 1) regardless of attribution are included as 'events' for the purpose of monitoring. The expected Grade 5 event rate is considered excessive if it exceeds 25%; therefore, we will call for immediate safety review in the event that the one-sided upper 90% exact binomial CI for the Grade 5 event rate, where the events are defined as above, exceeds 25%. Accrual to the study will be suspended immediately for the safety review and consideration of early study termination will be made. The one-sided upper 90% exact CI for the Grade 5 event rate will exceed 25% if 3 or more patients experience a Grade 5 event as defined above. Therefore, observation of a third Grade 5 event meeting the above criteria will immediately trigger the stopping rule; full accrual of 20 patients to the first stage need not happen in order for the safety review to take place.

10.2.3. Analysis Populations

10.2.3.1. Safety Population

The safety population will be used primarily for the analysis of safety data and will consist of all enrolled patients who receive 1 or more doses of glembatumumab vedotin (study drug). A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific safety parameter.

10.2.4. Efficacy Analysis

The eligible, treated population will be the basis for the primary analysis of efficacy in this study. Patients who discontinue study for reasons other than symptomatic deterioration or death prior to the first radiographic assessment will be considered unevaluable but will be included in the denominator when calculating the response rate. Every effort will be made to ascertain outcomes for all enrolled patients, irrespective of early discontinuation of protocol therapy.

A supportive analysis using the per-protocol population may be performed for the efficacy analysis. The per-protocol population excludes patients that experienced important deviations from the protocol that may substantially affect the results of the primary analysis. In addition, a baseline measurement and at least one follow-up measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific efficacy parameter. The final determination on protocol violations, and thereby the composition of the per-protocol population, will be made prior to locking the clinical database and will be documented in the statistical analysis plan.

10.3. Statistical Methods

10.3.1. Safety Analysis

Safety will be assessed by clinical review of all relevant parameters including adverse events, serious adverse events, laboratory values, vital signs, and ECGs results. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 10.2.3.1. The results of these analyses will be presented by study phase. For the escalation phase, tabulations will be provided by dose cohort and overall. Some safety analyses may be performed based on the dose escalation phase and Phase II study portion combined.

Summary tables and listings will be provided for all reported treatment emergent adverse events (TEAEs), defined as: 1) adverse events that start on or after the first administration of study drug; 2) pre-existing signs/symptoms that worsen after the first administration of study drug; 3) any AEs occurring within 28 days of last dose of study drug; and 4) SAEs related to study drug regardless of when the SAE started. The reported adverse event term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of subjects experiencing the event by MedDRA System Organ Class and Preferred Term. The causal relationship between the occurrence of an adverse event and study drug will be judged by the Investigator based on the conventions described in Section 8.2.2.1. In the event a patient experiences repeat episodes of the same adverse event, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- all TEAEs
- TEAEs by relationship (yes, no) to study drug and maximum severity grade
- TEAEs with action of study drug delayed/interrupted or treatment reduced
- TEAEs with action of study drug discontinued
- serious adverse events

For the escalation phase, the observed DLT rate in each dose cohort will be calculated by the crude proportion of patients in the escalation-evaluable population who experience DLT. The escalation-evaluable population includes patients who receive at least one dose of study drug and excludes patients who discontinue safety follow-up before day 42 (±3 days) for reasons other than DLT. Multiple concurrent adverse events leading to DLT will be considered a single DLT. The estimate of the DLT rate will be accompanied by a 2-sided 95% exact binomial confidence interval (CI). The relationship between the dose of study drug and the probability of DLT may be assessed in an exploratory manner by fitting various regression models such as Emax, logistic, and exponential model shapes.

All deaths that occur on study (defined as during treatment or within 28 days of treatment discontinuation) will be reported in a patient listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range as follows:

- Baseline value
- Minimum post-baseline value
- Maximum post-baseline value
- Average post-baseline value
- Last post-baseline value

Laboratory values will be assigned toxicity grades when available using the NCI-CTCAE scale. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

All patients will have pretreatment baseline vital signs and pre-dose measurements on Day 1 of each cycle. The results for each vital sign will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory values. For these analyses, the minimum, maximum, average, and last post-baseline value will be determined relative to the baseline vital sign measurements only. In addition, serial measurements will be obtained during and after each infusion of study drug. For each patient, the vital signs change from the pre-dose value will be summarized in a descriptive manner. The Wilcoxon signed rank test may be used to assist in the identification of any systematic changes.

10.3.2. Efficacy Analysis

The primary endpoint, ORR, will be estimated for eligible, treated patients enrolled in the Phase II study portion. The estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of confirmed CR or PR based on RECIST). The estimate of the ORR will be accompanied by a 2-sided exact 90% CI if the study stops early; if the study proceeds to a second stage then the CI will be computed using the methodology of Atkinson and Brown.

DOR will be calculated for patients who achieve confirmed CR or PR. For such patients, DOR is defined as the time from the start date of confirmed CR or PR (whichever response status is observed first), to the first date that recurrent or progressive disease or death is objectively documented.

PFS is defined as the time from the date of the first dose of study drug to the earliest of documented disease progression based on RECIST or death without prior progression. Patients not experiencing an event will be censored at their last adequate disease assessment date.

OS is defined as the time from the date of the first dose of study drug to the date of death (whatever the cause). Patients not experiencing an event will be censored at the last follow-up date.

DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 90% CIs calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996). The PFS rate and OS rate at selected landmarks and corresponding 90% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 90% CI.

For DOR and PFS, patients who meet one or more of the following conditions will be right-censored as follows:

- Patients with no baseline or post-baseline disease assessments unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event).
- Patients who initiate subsequent anticancer therapy in the absence of documented progression.
- Patients who die or have disease progression after missing 2 or more consecutively scheduled disease assessment visits.
- Patients who are last known to be alive and progression-free on or before the data cut-off date.

For such patients, the progression or censoring date will be determined based on described conventions (FDA 2007).

For OS, patients who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest diameters of target lesions. Exploratory analysis will be performed for the correlation between gpNMB expression and clinical outcomes.

11. LABORATORY AND PATHOLOGY CORRELATIVE STUDIES

11.1. Tumor Tissue Samples

11.1.1. gpNMB Expression (Mandatory)

Procurement of archived tumor tissue samples is mandatory to test for expression of gpNMB, by immunohistochemistry (IHC) at a central lab **(approximately 5 working day turnaround).** Archived tumor specimens obtained at any point in the course of disease are acceptable, but tumor specimens obtained in the setting of advanced (recurrent, locally advanced or metastatic) disease and subsequent to the last anti-cancer regimen received are preferred. Formalin-fixed paraffin-embedded (FFPE) diagnostic tumor tissue block(s) or 10-20 FFPE unstained, positively charged slides plus H&E slide from a tumor tissue block and copy of pathology report will be required.

Additional samples with pathology reports from previous collection dates should also be submitted when feasible. Submitted cytology samples such as pleural effusions, bronchial washings or fine needle aspirates (FNA) will be used to evaluate feasibility of gpNMB expression analysis and to investigate correlations with other samples for the patient, but they will not be used to determine study eligibility.

Any left-over samples will be banked for future research (optional).

11.1.2. Pharmacodynamics (Optional)

In the event of tumor resection, biopsy, or cytological sample collection anytime during treatment or following tumor progression, submission of these tissue samples and pathology reports is strongly encouraged. Analysis may include gpNMB expression by reverse transcriptase polymerase chain reaction (RT-PCR), examination of tumor markers using IHC or other molecular analyses, localization of glembatumumab vedotin, CR011 or MMAE at the tumor site and/or gpNMB expression levels in the tumor tissue, as well as evaluation of tumor infiltrating leukocytes and other immune response cells of interest. Any left-over samples will be banked for future research.

11.1.2.1. Tumor Tissue Sample Shipping

Samples should be shipped **Monday-Friday**. Samples will be shipped ambient via overnight courier.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits and instructions for sample collection, processing, storage and shipment will also be provided. Please see Laboratory Manual for detailed instructions.

11.2. Blood Samples

11.2.1. Immunogenicity

Peripheral blood will be obtained to monitor for the development of anti-glembatumumab vedotin and anti-CR011 antibodies, and whether these antibodies are neutralizing.

6 mL blood sample (red top tube) for serum will be collected prior to dosing on Day 1 of odd-numbered cycles (Cycle 1, Cycle 3, etc.) and at End of Treatment.

Any left-over blood samples will be banked for future research (optional).

11.2.2. Pharmacokinetics (PK)

Concentration of the antibody-drug conjugate (ADC), total antibody (TA) and free MMAE will be determined using GLP compliant enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The impact of circulating soluble gpNMB levels or other soluble molecules on pharmacokinetic parameters may also be examined.

6 mL blood sample (red top tube) for serum will be collected.

- Phase I
  - Day 1 of Cycles 1 and 2, prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion) and 4-5 hours after the end of infusion.
  - Cycle 1, Days 8 and 15.
  - Day 1 of Cycles 3 and 5 prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion).
  - End of Treatment visit.
- Phase II
  - Day 1 of Cycle 1, 2, and 5, prior to dosing and at end of infusion (at or within 10 minutes after completion of infusion).
  - End of Treatment visit.

Any left-over blood samples will be banked for future research (optional).

11.2.3. Pharmacodynamics

Serum and peripheral blood mononuclear cells (PBMC) samples will be obtained. Analysis may include (but not limited to) examination of gpNMB expression levels (and/or potential binding partners for gpNMB) on myeloid suppressor cells, as well as evaluation of peripheral leukocytes, circulating tumor cells and other immune response cells of interest. Soluble gpNMB levels in circulation may also be examined.

6 mL blood sample (red top tube) for serum and 20 mL blood sample (green top tubes) for whole blood will be collected prior to dosing on Cycle 1, Day 1, Cycle 2, Day 1 and at End of Treatment.

Any left-over blood samples will be banked for future research (optional).

11.3. Research Blood Samples Processing, Storage and Shipment

Kits and instructions for sample collection, processing, storage and shipment will also be provided. Please see Laboratory Manual for detailed instructions.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Red Top Tube Processing, Storage and Shipment

Gently mix the blood sample by inversion 8 times (do not shake). Allow the sample to sit at room temperature for 15-30 minutes until a clot has formed. If the blood is not centrifuged immediately after the clotting time (15 to 30 minutes at room temperature), the tubes should be refrigerated (4ºC) for no longer than 4 hours.

Once the clot has formed, the sample is ready for centrifugation. Centrifuge for 15 minutes at room temperature at 3000 RPM. Aliquot and store the resulting serum from each red top tube, as applicable per time point, into properly labeled polypropylene tubes as directed by the lab manual. Be careful to not disturb the clot. Store the samples in the freezer at ≤ -20°C or colder until they are shipped.

Samples should be batched and shipped quarterly or as requested by PrECOG. Ship samples **Monday-Wednesday**. Samples must be shipped on dry ice via overnight courier. Shipping labels, supplies and address will be provided.

Green Top Tube Processing and Shipment

Gently mix the blood sample by inversion 8 times (do not shake). Maintain and ship the same day at ambient temperature.

Sample collection should **ONLY** occur **Monday-Thursday**. Samples must be shipped via overnight courier. Shipping labels, supplies and address will be provided.

12. DATA HANDLING AND RECORD KEEPING

12.1. Data Quality Assurance

Monitoring and auditing procedures defined by PrECOG will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the electronic case report forms (eCRF) for completeness and clarity, cross-checking with source documents, clarification of administrative matters and drug accountability.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records. All the information required by the protocol should be provided; any omissions require explanation.

PrECOG will provide eCRFs via an electronic data capture (eDC) system for the recording and collection of data. Entries made in the eCRF must be verifiable against source documents. Corrections to eCRFs and source data will be made by authorized members of the study staff. The Investigator will sign the eCRFs to indicate that, to his/her knowledge, they are complete and accurate. An electronic audit trail will be maintained.

The Investigator will permit PrECOG direct access to source data/documents for trial-related monitoring, audits, review, and inspection(s). Through ongoing monitoring visits at the investigational sites, PrECOG will periodically check the patient data recorded in the eCRF's against source documents, to ensure accuracy, completeness, and adherence to the protocol, regulatory compliance, and the maintenance of comprehensive clinical records.

As well, the study may be audited by PrECOG and/or regulatory agencies at any time. If requested, the Investigator will provide PrECOG, applicable regulatory agencies and/or applicable ethical review boards with direct access to original source documents.

12.2. Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be reviewed, electronically signed, and dated by the Principal Investigator.

Instructions for management of patients who do not receive any protocol therapy:
If a patient is registered and does not receive any assigned protocol treatment, baseline, SAE and follow-up data will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate electronic off treatment form.

12.3. Archiving of Study Documentation

To enable evaluations and/or audits by regulatory authorities or PrECOG, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records), all signed informed consent forms, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence. The duration of record retention by the investigator should be according to International Conference of Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), PrECOG should be notified. The study records must be transferred to a designee acceptable to PrECOG, such as another investigator or another institution. The investigator must obtain PrECOG's written permission before disposing of any records, even if retention requirements have been met.

13. ETHICAL CONSIDERATIONS

13.1. Institutional Review Board or Independent Ethics Committee

ICH GCP guidelines require that all investigational drug studies be conducted under the auspices of an Institutional Review Board/Independent Ethics Committee (IRB/IEC). This committee, the makeup of which must conform to federal, state, and local guidelines regarding such, will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent. The Investigator will provide PrECOG with a copy of the communication from the IRB/IEC to the Investigator indicating approval/favorable opinion of the protocol and consent form. All changes to the protocol or consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients.

The Investigator will provide PrECOG with documentation of ethical review board approval of the protocol and the informed consent document *before* the study may begin at the investigative site(s). The Investigator will also be responsible for obtaining periodic IRB/IEC re-approval throughout the duration of the study. Copies of the Investigator's periodic report to the IRB/IEC and copies of the IRB/IEC's continuance of approval must be retained in the site study files and furnished to PrECOG.

The IRB/IECs must supply to PrECOG, upon request, a list of the IRB/IEC members involved in the vote and a statement to confirm that the IRB/IEC is organized and operates according to GCP and applicable laws and regulations.

13.2. Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). The Investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

13.3. Patient Information and Informed Consent

A sample Informed Consent Form will be provided. Prior to the beginning of the study, the Investigator must have the IRB/IECs written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to patients. The written approval of the IRB/IEC together with the approved patient information/Informed Consent Forms must be filed in the study files. The Informed Consent Form must contain all elements required ICH GCP Guidelines (E6) in addition to any other elements required by federal, state, local or institutional policy.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator will be responsible for obtaining an Informed Consent signed by each patient or his/her legally authorized representative, prior to his/her participation in the study, in accordance with ICH GCP guidelines. Informed Consent will be obtained from a patient or his/her legally authorized representative after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc., have been provided by the Investigator or designee, both verbally and in writing. The Investigator is responsible to see that informed consent is obtained from each patient or legal representative and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any

protocol procedures and prior to the administration of study drug. Participation in the study and date of informed consent given by the patient should be documented appropriately in the patient's files.

The original or copy of the signed Informed Consent must be maintained in the institution's records, and is subject to inspection by PrECOG or regulatory agencies. The patient or his/her legally authorized representative will also be given a copy of the signed consent form.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by patients or their legal representatives.

13.4. Protocol Amendments

Modifications to the study protocol will not be implemented by either PrECOG or the Investigator without agreement by each party and IRB/IEC approval/favorable opinion. However, the Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IRB/IEC/PrECOG approval/favorable opinion. The implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment, should be submitted to the IRB/IEC and PrECOG as soon as practical.

Any deviations from the protocol must be fully explained and documented by the Investigator. The circumstances, action taken and impact of the deviation on the trial must be communicated by the PI to PrECOG. Any subsequent actions will be assessed by PrECOG and documented.

13.5. Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the IRB/IEC according to local regulations. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

13.6. Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to PrECOG. Only the patient number and patient initials will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to PrECOG. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the PrECOG, IRB/IEC, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified.

14. REFERENCES

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Appendix 1: PrE0504 Eligibility Checklist

Each of the inclusion and exclusion criteria must be met in order for a patient to be considered eligible for this study. An eligibility checklist is provided to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

Phase I Only: Eligibility Criteria Checklist must be sent via fax (215-557-7169) or email (candrews@precogllc.org) to the PrECOG PM/designee for review and approval prior to subject registration. Site will receive a confirmation of approval. Once confirmation of approval is received subject can be registered.

PrECOG will not grant any exceptions or waivers to protocol eligibility criteria.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

PrECOG Patient No. _____

Patient's Initials (F, M, L) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the PrECOG Project Manager. Questions will be further discussed with the medical leads for the trial as deemed appropriate (e.g., medical monitor, study chair).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

INCLUSION CRITERIA

_____ 1. Read, understood, and provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.

_____ 2. Male or female patients with metastatic, histologically- or cytologically-confirmed Stage IIIB or IV non-small cell lung cancer (NSCLC) of squamous histology (Staging per American Joint Committee on Cancer [AJCC], Edition 7). Mixed histology adenosquamous NSCLC will also be permitted.

_____ 3. Experienced progression/recurrence of disease during or subsequent to the most recent anti-cancer regimen.

_____ 4. Any number of prior lines of systemic therapy may have been received for advanced (recurrent, locally advanced, or metastatic) SCC of the lung, but at least one must have been a platinum-based chemotherapy regimen. Platinum therapy may be given on-label or as part of a clinical trial.

_____ 5. Lung cancer confirmed to express gpNMB, as assessed by immunohistochemistry at a central lab (using expression in ≥ 5% of tumor epithelial cells as a cut-off for positivity). This can be tested on archived tissue if available, although preferred tumor specimen is a biopsy after the most recent therapy.

NOTE: Additional samples from previous collection dates should also be submitted when feasible. Submitted cytology samples such as pleural effusions, bronchial washings or fine needle aspirates (FNA) will be used to evaluate feasibility of gpNMB expression analysis and to investigate correlations with other samples for the patient, but they will not be used for determination of study eligibility. For patients with multiple samples submitted, eligibility will be

based on the most recently obtained sample, or, if obtained on the same date, the sample with the highest level of gpNMB expression. However, in the event that disparate results are obtained for samples received within a similar timeframe (i.e., within a 6-month period), the medical monitor may be consulted for determination of eligibility.

_____ 6. Age ≥ 18 years.

_____ 7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (Appendix 2).

Performance Status: _____ Date of Assessment: _____

_____ 8. Measurable disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) [Appendix 3]. Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.

_____ 9. Resolution of all toxicities related to prior therapies to ≤ NCI-CTCAE Grade 1 severity or back to baseline, except for alopecia, vitiligo, or endocrinopathies on replacement therapy.

_____ 10. Adequate bone marrow function as assessed by:

- Absolute Neutrophil Count (ANC) ≥ 1500/mm^3

ANC: _____ Date of Test: _____

- Hemoglobin ≥ 9.0 g/dL

Hemoglobin: _____ Date of Test: _____

- Platelets ≥ 100,000/mm^3

Platelets: _____ Date of Test: _____

_____11. Adequate renal function as assessed by:

- Serum Creatinine ≤ 2.0 mg/dL

Serum Creatinine: _____ Date of Test: _____

- Calculated (Cockcroft and Gault Formula Appendix 4) or 24-Hour Urine Creatinine Clearance >40 mL/min

Creatinine Clearance: _____ Date of Test: _____

_____12. Serum albumin ≥ 3 g/dL.

_____13. Adequate liver function as assessed by:

- Total Bilirubin ≤ 1.5x upper limit of normal (ULN)

Total Bilirubin: _____ ULN: _____ Date of Test: _____

- Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5x ULN (≤ 5.0x ULN in patients with liver metastases)

ALT: _____ ULN: _____ Date of Test: _____

AST: _____ ULN: _____ Date of Test: _____

NOTE: Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.

NOTE: The liver is a route of clearance for MMAE. Patients with mild hepatic impairment are excluded from Phase I (the dose escalation portion) to minimize the influence of hepatic impairment on tolerability and dose selection because a lower dose is recommended for other ADCs with a vc-MMAE moiety. **See the acceptable liver function parameters for Phase I defined above.** In Phase II (the dose expansion portion), a lower starting dose for patients with mild hepatic impairment will be determined based on the MTD recommended from the Phase

I portion of this trial. **The acceptable liver function parameters will be redefined for Phase II.**

_____ 14. Both male and female patients of childbearing potential enrolled in this trial must use adequate birth control measures during the course of the trial and for at least one month after discontinuing study drug. Adequate birth control measures are defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, or intrauterine device), implants, injectables, combined oral contraceptives, sexual abstinence (abstinence from intercourse during the ovulation period), or vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.

_____ 15. Willing to provide blood samples for research purposes (Section 11.2).

EXCLUSION CRITERIA

_____ 1. Received glembatumumab vedotin (CR011-vcMMAE; CDX-011) or other MMAE-containing agents previously.

_____ 2. Chemotherapy within 21 days or at least 5 half-lives (whichever is shorter) prior to the planned start of study treatment; radiation outside the thorax within 14 days prior to the planned start of study treatment or thoracic radiation; antibody based therapy or investigational therapy within 28 days prior to the planned start of study treatment.

_____ 3. Neuropathy >NCI-CTCAE Grade 1.

_____ 4. Subjects with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin. Compounds of similar composition include Auristatin PHE as an anti-fungal agent, Auristatin PE (TZT-1027, Soblidotin, NSC-654663) as an anti-tumor agent and Symplostatin 1 as an anti-tumor agent.

_____ 5. Known brain metastases, unless previously treated and patients are neurologically returned to baseline except for residual signs and symptoms related to CNS treatment and CNS lesions are not progressive in size and number for 4 weeks.

_____ 6. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, and congestive heart failure (New York Heart Association (NYHA) Class 3 or 4 [Appendix 5]) related to primary cardiac disease, a history of a serious uncontrollable arrhythmia despite treatment, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry.

_____ 7. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary.

NOTE: Microscopic examination of urinalysis is required during screening. If urinary infection is suspected, a negative urine culture is required prior to enrollment.

_____ 8. Subjects on immunosuppressive medications such as azathioprine, mycophenolate mofetil, cyclosporine or require chronic corticosteroid use (defined as ≥ 3 months of prednisone dose equivalent of ≥ 10 mg).

_____ 9. The MMAE component of glembatumumab vedotin is primarily metabolized by CYP3A. Patients taking strong CYP3A inhibitors and inducers are excluded in Phase I (the dose escalation portion) to minimize the effect of these modulators on exposure, tolerability and dose selection (http://medicine.iupui.edu/clinpharm/ddis/main-table/).

_____ 10. History of other malignancy except for adequately treated basal or squamous cell skin cancer, curatively treated in situ disease, or any other cancer from which the patient has been disease-free for ≥ 2 years.

_____ 11. Pregnant or breast-feeding women.

Is the patient a woman of childbearing potential? _____ (yes/no)

If yes, Date of Test: _____ Results: _____

_____ 12. Subjects must not be on home oxygen therapy (intermittent or continuous).

_____ 13. Any underlying medical condition that, in the Investigator's opinion, will make the administration of study treatment hazardous to the patient, or would obscure the interpretation of adverse events.

Appendix 2: ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix 3: RECIST 1.1 Criteria

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination, unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. ("Methods of Lesion Measurement" for further guidance.)

Only patients with measurable disease on baseline evaluations should be included. (Measurable disease is defined by the presence of at least one measurable lesion; see "Measurability of Tumor at Baseline".) At baseline, lesions should be identified as either "Target" or "Non-Target" as follows:

Target Lesions:

- Up to a maximum of five measurable target lesions total (with a maximum of two target lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. (This means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded.)
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- All target lesion measurements should be recorded in metric notation, using calipers if clinically assessed.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. ("Tumor Response Evaluation")

Non-Target Lesions:

- All other measurable/non-measureable lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. It is acceptable to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').
- Non-target lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. ("Tumor Response Evaluation") While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively.

MEASURABILITY OF TUMOR AT BASELINE

- Measurable: Tumor lesions 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 scan slice thickness no greater than 5 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20 mm by chest x-ray.

  Note: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (for lymph nodes, only the short axis is measured and followed).
- Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

- Malignant Lymph Nodes: Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. At baseline and in follow-up, only the short axis will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.
- Bone Lesions: Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Cystic Lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS OF LESION MEASUREMENT

- Clinical Exam: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest X-Ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression. (“Tumor Response Evaluation”)
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor Markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.
- Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

TUMOR RESPONSE EVALUATION

Evaluation of Target Lesions:

Target lesions will be assigned an overall response assessment at each evaluation time point according to the following definitions:

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of 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 5 mm. (**Note:** the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

- Lymph Nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target Lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (**Note:** It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions:

Non-target lesions will be assigned an overall response assessment at each evaluation time point according to the following definitions:

- *Complete Response (CR):* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease (PD):* Unequivocal progression (special notes below) of existing non-target lesions. (**Note:** the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease:

- When the patient also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions:

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important.

- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

- While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. (A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.)
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Overall Response:

It is assumed that at each protocol specified time point, an overall response assessment occurs. The patient's overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Appendix 3 Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, **Appendix 3 Table 2** is to be used.

Special notes on evaluation of overall response:

- Missing assessments and inevaluable designation:
  – When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
  – If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.
- 'Symptomatic deterioration': Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Appendix 3 Tables 1 & 2**.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.
- Confirmation of response: In the event of complete or partial responses, efforts should be made to obtain a confirmatory scan (no sooner than 28 days later).

Appendix 3 Table 1: Overall Response: Patients with Target +/–Non-Target Disease.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not All Evaluated	No	PR
SD	Non-PD or Not All Evaluated	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Appendix 3 Table 2: Overall Response: Patients with Non-Target Disease Only.

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not All Evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

FREQUENTLY ASKED QUESTIONS

What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?

Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters.

How large does a new lesion have to be to count as progression? Does any small sub-centimeter lesion qualify, or should the lesion be at least measurable?

New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artifact with the support of the radiologists.

How should one lesion be measured if on subsequent exams it is split into two?

Measure the longest diameter of each lesion and add this into the sum.

Does the definition of progression depend on the status of all target lesions or only one?

As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum.

What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?

RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness.

What should we record when target lesions become so small they are below the 10 mm 'measurable' size?

Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded.

If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?

Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD.

When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?

The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up). The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up.

Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used). What is the effect this has on the other target lesions and the overall response?

What may be done in such cases is one of the following:

(a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable.

(b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability.

(c) If neither (a) nor (b) is possible then it is a judgment call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel.

It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favor of a response.

What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?

Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding.

A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?

It is not infrequent that tumor shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD.

A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?

CT scan. Always follow by imaging if that option exists since it can be reviewed and verified.

A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?

The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect.

If I am going to use MRI to follow disease, what is minimum size for measurability?

MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Can PET–CT be used with RECIST?

At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Adapted from Eisenhower 2009 (Eisenhauer, Therasse et al. 2009)

Appendix 4: Cockroft and Gault Formula

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [years]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

Appendix 5: NYHA Classification

Class	Symptoms
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford Textbook of Internal Medicine. Vol. 2, pp 2228. Oxford University Press. 1997	

Appendix 6: Investigator Signature

1. I have carefully read this protocol entitled **"**A Phase I/II Study of Glembatumumab Vedotin in Patients with gpNMB-Expressing, Advanced or Metastatic Squamous Cell Carcinoma of the Lung**"**, **Version 3.0 dated 11/14/2017 (Protocol Number PrE0504)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.
3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.
5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the FDA.

Principal Investigator (PI):

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

MM DD YYYY