Statistical Analysis Plan

Protocol	PrE0504
Version	Final 1.0
Date	28 October 2016

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

DOCUMENT:	Statistical Analysis Plan
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1. LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
ACS	American Cancer Society
ADC	Antibody-Drug Conjugate
AE	Adverse event
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

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
IgG2	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	Monoethylauristatin 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
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

2. INTRODUCTION

2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the data collected in the Phase II of this study. A detailed description of the planned tables, figures and listings (TFLs) to be

presented in the Clinical Study Report (CSR) is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy of data collected in Phase II of the study and to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and QDS. A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. Attached signatures indicate approval of the safety and statistical analyses sections of the SAP. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for generation of the TFLs that will be the basis of the safety results described in the clinical study report.

Deviations from this SAP, both substantial and non-substantial, will be documented in the CSR. All deviations from the SAP and/or TFL templates will be documented in a running Addendum to the SAP document and finalized with signoff as an addendum to the SAP prior to database lock.

3. STUDY OBJECTIVES

3.1. Primary Objective

- Phase I: To evaluate the safety and tolerability and determine the Maximum Tolerated Dose (MTD) of glembatumumab vedotin in patients with advanced gpNMB-expressing Squamous Cell Carcinoma (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.

3.2. Secondary Objective

- 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).

3.3. Exploratory Objective

- 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 Monoethylauristatin 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.

4. STUDY DESIGN

4.1. General Study Design and Treatment Plan

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	1.3	3-6
	1	1.9	3-6
	2	2.2	3-6
Phase II	Stage 1	MTD*	20
	Stage 2	MTD*	15

* MTD as determined during the dose-escalation phase

Subjects will receive study drug, 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 6 (±1) weeks for six months, and every 9 (±2) weeks thereafter, until progression. Tumor response will be assessed by the investigator in accordance with RECIST 1.1 guidelines. Subjects who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies.

The MTD for the dose-escalation phase will be the highest dose-level where 0/3, or 1/6 subject experienced a Dose-Limiting Toxicity (DLT).

4.2. Study Population

Subjects with gpNMB-Expressing, Advanced or Metastatic SCC of the Lung, who have failed a prior platinum-based chemotherapy regimen. All subjects have to meet all inclusion and exclusion criteria in order to be eligible for participation of study.

Subjects that participated in Phase I will not be eligible to participate in Phase II.

Number of subjects: Phase I will enroll up to 12 subjects and Phase II will enroll up to 35 subjects. There will be 20 subjects enrolled in Phase II Stage 1 initially and another 15 subjects will be enrolled in Stage 2. There may be additional 2 subjects needed to ensure sufficient eligible and treated subjects. In Phase II, subjects 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. Approximately up to 49 subjects will be enrolled.

MTD evaluable subjects: In Phase I, subjects 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.

Safety analysis population: The safety population will be used primarily for the analysis of safety data and will consist of all enrolled subjects who receive at least 1 study drug. It includes Phase I and Phase II all subjects.

Efficacy analysis population: Phase II subjects who receive at least 1 study drug and are eligible will be defined as efficacy analysis population.

Per-protocol analysis population: Subjects who are in efficacy analysis population, have a baseline and at least 1 follow-up measurement after study treatment, and also do not have major protocol deviation and violation are considered as per-protocol analysis population. PrECOG will provide a list of important deviations and protocol violations that will used to determine per-protocol population before database locking. This population may use for supportive analysis for certain efficacy parameters.

Pharmacokinetics (PK) analysis population: Phase I and Phase II Subjects who have adequate PK samples and results collected will be included in the PK analysis population.

Pharmacodynamics (PD) analysis population: Phase I and Phase II Subjects who have adequate PD samples and results collected will be included in the PD analysis population.

4.3. Duration of Study Treatment, Follow-up and End of Study

Treatment phase: Subjects will start study treatment within 10 working days from registration until disease progression or intolerance. Phase I subjects have to complete DLT evaluation period, at the end of cycle 2 (Day 42 ± 3 days) in order for MTD determination.

Survival Follow-Up: Subsequent to progression of disease, all subjects will be followed until study closure.

Subject Complete study: subjects who die or complete the study follow-up through study closure will be considered to have completed the study.

The study completion: 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 subject discontinues study treatment.

It is anticipated that the enrollment period will be approximately 30 months (Phase I: 12 months and Phase II: 18 months). All subjects will be followed with regard to survival until death, discontinuation from study follow-up, or termination/completion of study.

Premature termination of this study may occur because of a regulatory authority decision, drug safety issues, or at the discretion of PrECOG.

4.4. Criteria for discontinuation from Study Treatment

Subjects will receive protocol therapy unless:

- Progressive disease, as assessed by the treating investigator in accordance with RECIST 1.1 criteria.
- Symptomatic deterioration (clinical progression);
- Receipt of alternate anti-cancer treatments;
- Intercurrent illness that prevents further administration of treatment per investigator discretion;
- Withdrawal request by the subject or the subject's legal representative;
- Unacceptable adverse event, including the development of DLT
- Physician Decision;
- Non-compliance of the subject;
- Pregnancy;
- Death, otherwise not explainable by the above options;
- Subject lost to follow-up.

5. GEBERAL STATISTICAL CONSIDERATIONS

Statistical analysis and programming of tables, listings and figures will be conducted by QDS, using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

All analyses will base on the approved final version of this statistical Analysis Plan (SAP).

The analyses described in this SAP are applicable for the planned TFLs mockup listed in separate documents.

5.1. 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 Antibody-Drug Conjugate (ADC), Total Antibody (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

5.2. Methodology

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies and percentages.

Listings will be presented by subject and all data will be presented. Tables will be presented by overall subjects and only data pertaining to the specific population being analyzed will be used.

5.3. Handle Missing, Unscheduled and Repeated Measurements Data

If AE start date is missing, then the first study treatment date will be assumed. If AEs with missing relationship, it will be considered study drug related.
If other data have missing or invalid values, they are treated as missing and no imputation needed.

In summary statistics, if there are repeated post-baseline measures in laboratory and vital signs safety data, the average value will be used to represent that time point measurements for continuous data, and the worst value for categorical data.

Unscheduled safety measurements will be included in the summary statistics and also will be displayed in data listing. Baseline will include unscheduled measure in the baseline selection algorism. The unscheduled efficacy variables, such as tumor assessment will be treated as the same as planned measurement.

Clinical visits from CRF will be used for by-visit analysis. If the visit date outside of protocol defined visit window, data inquiry will be performed to confirm the data.

5.4. Interim Analysis and Data monitoring

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 protocol Section 10.2.

At end of stage 1, after 20 eligible subjects enrolled, and treated, if ≥2 subjects achieve a complete response (CR) or partial response (PR), then stage 2 will open to enroll 15 additional eligible subjects.

A group of key efficacy and safety analysis TFLs will be provided in the interim analysis.

6. STUDY POPULATION CHARACTERISTICS

6.1. Subject Disposition

The number of subjects enrolled in the study, inevaluable subjects, completing the therapy will be tabulated by study phase for overall, and will be listed by subject. Subject status will be summarized at the end of study. End of treatment summary will indicate number of subjects who completed treatment and subject status for those who discontinued early. The percentage for eligible subjects and inevaluable subjects are based on enrolled subjects.

6.2. Protocol Deviation and Violation

Protocol deviations and violation will be summarized using descriptive statistics by protocol deviation classification, visit, and module for overall subjects.

The determination of protocol violations will be made prior to clinical database lock by PrECOG. QDS will incorporate this information to consist of Per-protocol population in database.

If any protocol violation and eligibility inclusion or exclusion exceptions occur, they will be listed by subject with the same inclusion/exclusion number stated in the protocol.

If there are any subjects who were registered but not eligible and not treated, they will be displayed in the data listing with the reasons.

6.3. Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, race, height, weight, and study phase) will be listed and summarized overall using descriptive statistics (mean, standard deviation, median, minimum, and maximum for a numerical variable, and frequency counts / percentages for categorical variable). In addition to demographics, the following baseline characteristics will be summarized using descriptive statistics and listed by subject: Cancer diagnosis and staging, prior therapy, medical surgical history, ECOG performance status, and baseline tumor assessment.

6.4. Dosing and Extent of Exposure

Study drug will be administered on Day 1 of each 21 day cycle. Subjects will continue to be dosed once every 3 weeks. Treatment may be delayed for up to 3 weeks, if more than 3 weeks is required, PrECOG will determine whether subject continue to be treated. If treatment delayed, the subsequent treatments will maintain 3-week cycle interval.

There are 3 dose levels in Phase I and only 1 dose level, MTD dose in Phase II.

Dose adjustments are permitted but a maximum of 2 dose reductions are allowed. Dosing below 1.0 mg/kg will not be allowed.

Descriptive statistics of treatment cycle and dose exposure will be provided. Data listing for subject treatment exposure will be produced as well.

6.5. Medical History and Cancer therapy

Medical, surgical history and existing symptoms will be summarized by study phase. Data will be also displayed in listing format.

6.6. Concomitant Medications

Concomitant medications are that 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. All concomitant medications will be coded by current version of WHO Drug Dictionary.

Concomitant medication will be summarized by ATC classification and WHO Drug Dictionary preferred term. A data listing will also be presented.

7. MEASUREMENT OF EFFECT

7.1. Efficacy Analysis

Efficacy analysis include objective response rate (ORR), duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS).

7.2. Primary Endpoint Assessment

ORR, the primary endpoint, will be estimated for eligible, treated subjects 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 subjects 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 repeated 90% CI.

The subject'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.

The best overall response is the best response recorded from the start of the treatment until end of study. The order of response from best to worst is: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Inevaluable (NE) and Progressive Disease (PD). It includes scheduled and unscheduled tumor assessments. Only confirmed CR and PR are considered as response for ORR analysis.

The details about tumor response criteria for target, non-target and new lesions are included in protocol Appendix 3.

7.3. Secondary Endpoint Assessment

DOR is defined as the time from the start date of 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.

OS is defined as the time from the date of the first dose of study drug to the date of death (whatever the cause).

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. 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, subjects who meet one or more of the following conditions will be right-censored as follows:

- Subjects 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).
- Subjects who initiate subsequent anticancer therapy in the absence of documented progression.
- Subjects who die or have disease progression after missing 2 or more consecutively scheduled disease assessment visits.
- Subjects who are last known to be alive and progression-free on or before the data cut-off date

For OS, subjects 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 subjects' date of last contact or data analysis cutoff date, whichever event occurs first.

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.

8. SAFETY MEASUREMENTS

Safety is to be evaluated by

- 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

Safety will be assessed by clinical review of all relevant parameters including adverse events, serious adverse events, laboratory values, vital signs, physical exam, ECOG performance status, and ECGs results. Unless specified otherwise, the safety analyses will be conducted for the safety population. 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.

8.1. Adverse Events

Treatment emergent adverse events (TEAEs) is 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.

If the AE onset date is unknown, then the date of first administration of study drug will be used.

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. In the event a subject 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

All deaths that occur on study (defined as during treatment or within 28 days of treatment discontinuation) will be reported in a subject 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

AE Severity:

CTCAE grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting.

AE relationship to study drug

The causal relationship between the occurrence of an adverse event and study drug will be judged by the Investigator and recorded in CRF page in the options of "unrelated" and "related". AEs with missing relationship will be considered study drug related.

The following by subject data listings will be prepared: subjects with serious adverse events, subjects with treatment-related adverse event, adverse events leading to discontinuation of study treatment and subjects with Grade 5 adverse events.

8.2. Laboratory assessment

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 subjects 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.

8.3. Vital Sign

All subjects 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. The change from baseline at each treatment cycle will be also summarized.

Baseline of vital sign is defined as the last measurement during screening period. If screening measurement is missing, the pre-dose measurement on Day 1 will be used for baseline.

In addition, serial measurements will be obtained during and after each infusion of study drug. For each subject, 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.

8.4. Other safety data

Physical examination, ECG and ECOG performance status are also performed during the study to measure the safety and tolerability of study drug.

The summary statistics and change from baseline will be performed by each scheduled visit for these parameters.

If any screening (baseline) safety data are repeated, the measurement taken closest to dosing will be used in the analysis. Baseline will be defined as the last non-missing result, including results from repeated and unscheduled measurements, before dosing. If there are repeated measurements at a time point after dosing, the average value at that time point will be used in the summary tables for continuous data, and worst value for categorical data.

9. EXPLORATORY ENDPOINTS ASSESSMENT

9.1. Efficacy variables and degree of gpNMB expression

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.

9.2. Pharmacokinetics (PK) Analysis

To further characterize the pharmacokinetics and immunogenicity of glembatumumab vedotin in this subject population.

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.

Descriptive statistics for the concentration of PK variables by study drug dose level will be provided. Concentration data listing will be displayed by subject and time points.

9.3. Pharmacodynamics (PD) Analysis

To examine pharmacodynamic effects of treatment, including tumor immune cell infiltrate type and number; localization of glembatumumab vedotin, CR011 or Monoethylauristatin E (MMAE) at the tumor site; soluble mediators and/or gpNMB expression levels in tumor tissue; and analysis of peripheral blood cell subsets.

Serum and peripheral blood mononuclear cells (PBMC) samples will be obtained. Analysis may include examination of gpNMB expression levels 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.

Descriptive statistics for gpNMB expression level, leukocytes, and circulating tumor cell by study drug level may be performed. Data listing will be provided.

10. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value, and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Section 14 tables and Section 16 Listings should be in landscape format with Courier New 9 pt. font. Output should adhere to margins of: top - 1.0 in, bottom - 1.0 in, right - 1.0 in, and left - 1.0 in). For item 14 tables, a blank row will separate the header from the content of the table listing. For tables that have "n (%)", the placement should be centered below "N=xx" in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, the corresponding percentage should be indicated as 0.

- SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "SD", and presented below the mean value. The SD should have one additional decimal place beyond that of the mean (e.g., mean has one decimal place, SD should have two).

- If the table or listing is too long to display on one page, the additional (treatment) columns will be continued on the following pages.

- "N" will represent the entire population group being analyzed, while "n" will represent a subset of "N". For tables with population designated as a row heading, "N" should be used (i.e., tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator, it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- All data listings will be sorted by Subject Number and parameter or time point (as applicable).

- The date format for all dates is DDMMMYYYY.

- If no data are collected for use in the tables and listings, then a table and/or listing will be created stating that no data are available.

- A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

- The footnotes should contain three lines at the bottom end. a) Program Source b) Output Path and c) Source Data.

Visit	Screening 2		Treatment Visits3					Disease Assessment Visit6	Survival Assessment7
		Cycle 1/ Day 1	Cycle 1/ Day 84	Cycle 1/ Day 154	Cycle 2/ Day 1	Cycle 3 onward/Day 1	End of Treatment5		
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 Tissue8	X9						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]

11. APPENDIX: SCHEDULE OF ASSESSMENTS1

Table - 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).** 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.