STATISTICAL ANALYSIS PLAN

Protocol CDX011-05
A Phase II Study of Glembatumumab Vedotin, an Anti-gpNMB Antibody-Drug Conjugate, as Monotherapy or in Combination with Immunotherapies in Patients with Advanced Melanoma

IND#: 74907

Version: Final v1.0
Date: Jan 22th, 2018

This document is prepared according to protocol amendment 3, dated November 17th, 2016.

TABLE OF CONTENTS

LIST OF TABLES

LISTING OF ABBREVIATIONS

ADaM	Analysis Data Model
ADC	Antibody-Drug Conjugate
ADI	Actual Dose Intensity
AE	Adverse Event
ALT (SGPT)	Alanine Transaminase (Serum Glutamic Pyruvate Transaminase)
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CPI	Checkpoint Inhibitor
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
FDA	Food and Drug Administration
GpNMB	Glycoprotein NMB
HRQOL	Health-Related Quality of Life
IHC	Immunohistochemistry
irRECIST	Immune-Related RECIST
ITT	Intention-to-Treat
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute (of the United States)
NE	Not Evaluable

ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic / Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response / Progesterone Receptor
PS	Performance Status
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
ROC	Receiver Operating Curve
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation / Stable Disease
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLG	Tables, Listings, and Graphs
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned data analysis specifications for Protocol CDX011-05, "A Phase II Study of Glembatumumab Vedotin, an Anti-gpNMB Antibody-Drug Conjugate, as Monotherapy or in Combination with Immunotherapies in Patients with Advanced Melanoma" for the completion of the Clinical Study Report (CSR).

This is an open-label Phase II study of glembatumumab vedotin administered at a starting dose of 1.9 mg/kg, as monotherapy or in combination with the agonist anti-CD27 antibody, varlilumab, or PD-1 targeted checkpoint inhibition (nivolumab or pembrolizumab), in patients with unresectable Stage III or IV melanoma who have previously received CPIs. This study consists of 3 cohorts (Table 1).

Table 1 Cohorts in Study CDX011-05

Cohort	Treatment	Glembatumumab Vedotin	Varlilumab	PD-1 CPI Dose	Patients (n)
1	Glembatumumab vedotin	1.9 mg/kg	-	-	Approx. 60
2	Glembatumumab vedotin + Varlilumab	1.9 mg/kg	3.0 mg/kg	-	Approx. 30
3	Glembatumumab vedotin + PD-1 targeted CPI	1.9 mg/kg	-	As per institutional standard of care with reference to the package insert	Approx. 30

Tumor assessments will be performed every 6 weeks (±1 week) for the first 6 months, and every 9 weeks (±2 weeks), thereafter, until documented progression of disease or initiation of alternate anticancer therapies. Tumor response will be assessed by the investigator in accordance with RECIST 1.1 guidelines (Appendix 3) (Eisenhauer, Therasse et al. 2009). For Cohorts 2 and 3, supplementary retrospective analyses of tumor response and progression may also be performed using Immune-Related RECIST ("irRECIST") criteria (in which new lesions do not constitute progression, but contribute to the calculated sum of diameter of all measurable disease) (Nishino, Giobbie-Hurder et al. 2013). 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 Cohorts 2 and 3, in cases of apparent progression that may reflect enhanced inflammation and/or an initial imbalance in the kinetics of tumor growth and anti-cancer immune activity, continued combination treatment may be allowed with consent of the patient and permission granted from the Celldex Medical Monitor, until a second radiologic confirmation of progression performed at the next scheduled disease assessment (or sooner if clinically indicated). In addition, the following criteria must be met: 1) the patient experiences Investigator-assessed clinical benefit; and 2) the patient is tolerating the study treatment. Refer to Appendix 1 for the detailed schedule of assessments.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary objective(s)

The primary objective of the study is to evaluate the anti-cancer activity of glembatumumab vedotin as monotherapy and in combination with varlilumab, or in combination with a PD-1 targeted checkpoint inhibitor (CPI), in advanced melanoma as measured by the objective response rate (ORR) per RECIST 1.1.

2.1.2 Secondary objective(s)

- To further assess the anti-cancer activity of glembatumumab vedotin as monotherapy and in combination with varlilumab, or in combination with a PD-1 targeted CPI, in advanced melanoma, as assessed by progression free survival (PFS), duration of response (DOR) and overall survival (OS)
- To investigate if the anti-cancer activity of glembatumumab vedotin as monotherapy and in combination with varlilumab, or in combination with a PD-1 targeted CPI, in advanced melanoma is dependent upon the degree of gpNMB expression in tumor tissue
- To further characterize the safety of glembatumumab vedotin as monotherapy
- To characterize the safety of the combination of glembatumumab vedotin with varlilumab, or in combination with a PD-1 targeted CPI, in advanced melanoma

2.1.3 Exploratory objective(s)

- To examine the range of gpNMB expression in advanced melanoma, and to assess whether gpNMB expression changes over time and/or with specific prior therapies
- To examine pharmacodynamic effects of treatment, including types and number of immune cells infiltrating the tumor; localization of glembatumumab vedotin, CR011, and MMAE in the tumor; soluble mediators, gpNMB expression levels and/or other potential biomarkers in both normal and tumor tissue; and analysis of peripheral blood subsets
- To further characterize the pharmacokinetics and immunogenicity of glembatumumab vedotin and varlilumab in patients with advanced melanoma, and to explore the relationships between patient-specific measures of exposure and safety and activity parameters
- To assess the anti-cancer activity of the combination of glembatumumab vedotin and varlilumab, or the combination of glembatumumab vedotin with a PD-1 targeted CPI, as measured by the ORR and PFS per irRECIST

2.2 Study Endpoints

2.2.1 Primary endpoint(s)

Efficacy

- Objective response rate (ORR), defined as the proportion of patients whose best overall tumor response are confirmed complete response or partial response by RECIST 1.1.

2.2.2 Secondary endpoint(s)

Efficacy

- Duration of response (DOR), defined as the time from response criteria are first met for either complete response (CR) or partial response (PR), until the first date that

progressive disease (PD) is objectively documented, or until death (if death occurs within 9 weeks of the last evaluable scan), for subjects who achieve confirmed CR or PR.

- Progression-free survival (PFS), defined as the time from first dose of study treatment date to first documentation of objective progression or death due to any cause, whichever occurs first.
- Overall survival (OS), defined as the time from first dose of study treatment to death due to any cause.

Safety Endpoints

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

2.2.3 Exploratory endpoint(s)

Efficacy

- Immune-*related RECIST ORR and PFS (Cohorts 2 and 3)*

Correlative:

- Concentration of antibody-drug conjugate(ADC), total antibody (TA), and free Monomethyl auristatin E (MMAE).
- Pharmacodynamic parameters, including gpNMB expression levels and other biomarkers in serum and both normal 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. Additional analysis may include immune response assessment to potentially relevant tumor antigens.

3 DETERMINATION OF SAMPLE SIZE

Three cohorts of patients will be enrolled and treated. In Cohort 1, approximately 52 evaluable patients may be enrolled and treated with glembatumumab vedotin monotherapy with objective response rate (ORR) as the primary endpoint. As patients who discontinue study prior to the first disease assessment without symptomatic deterioration or death will not be evaluated and will be replaced, it is anticipated that approximately 60 patients will be enrolled in this cohort.

For Cohort 1, the sample size was determined to estimate the ORR with one-sided significance level of 5% and power of 80%, using exact binomial test, to determine if the ORR exceeds a predefined minimum. A sample size of 52 patients will test the null hypothesis of an ORR of 5% versus 15% under the alternative hypothesis. If the number of responses (CR or PR) is 6 or more, the null hypothesis will be rejected with the actual error rate of 0.045. If the number of responses is 5 or less, the alternative hypothesis will be rejected with an actual error rate of 0.188.

For Cohorts 2 and 3, ORR by RECIST 1.1 remains the primary endpoint. Supplementary analyses of tumor response and progression may also be performed using irRECIST criteria (in which new lesions do not necessarily constitute progression, but contribute to the calculated sum of diameter of all measurable disease) (Nishino, Giobbie-Hurder et al. 2013).

For Cohorts 2 and 3, 30 patients per cohort, to achieve 25 evaluable, will be enrolled to have the maximum width of the 95% confidence interval (CI) of the estimated ORR to be no greater than 41%. If 7, 8, or 9 responses are observed (i.e., the estimated ORR is 28%, 32%, or 36%) among the 25 evaluable patients, then the lower limits of the two-sided 95% CIs of the estimated ORR are 12%, 15%, and 18% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals. As a secondary consideration, 25 evaluable patients can achieve 90% power for ORR of 25% comparing to 5% and 79% power comparing to 10% ORR with 1-sided type I error of 0.1 based on exact binomial test. Patients in Cohorts 2 and 3 who experience an event determined to be a treatment-limiting toxicity will not be replaced and will be considered evaluable.

4 ANALYSIS POPULATIONS

The three treatment cohorts will be analyzed separately.

4.1 Safety Population

The safety population will include all patients who receive at least one dose of study treatment of glembatumumab vedotin or varlilumab or a PD-1 targeted CPI. 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. For each cohort, the safety population constitutes all treated patients and will be used for secondary analyses of ORR and all other endpoints. The safety population is equivalent to the ITT population defined in the protocol.

4.2 Response Evaluable Population

Response evaluable population includes subjects who have measurable disease at baseline and receive study treatment, and excludes subjects who discontinue study prior to the first disease assessment without symptomatic deterioration or death. Specifically, patients who discontinue study prior to the first disease assessment for reasons unrelated to study treatment (i.e., adverse events deemed unrelated to study treatment, withdrawal of consent, lost to follow-up, withdrawal due to administrative reasons, etc.) will be excluded from the response-evaluable population and may be replaced. Patients who discontinue study prior to the first disease assessment due to treatment-related adverse events, symptomatic deterioration (adverse events due to progression), or death will be included in the response evaluable population. The primary ORR analysis is based on evaluable population and the secondary analysis will be based on safety (treated) population.

4.3 Per-protocol Population

The per-protocol population, as a subset of Safety Population, excludes subjects who experienced important deviations from the protocol that may substantially affect the results of the primary analysis. A supportive analysis using the per-protocol population may be performed for efficacy. The final determination on important protocol deviations, and thereby the per-protocol population, will be made prior to locking the clinical database.

5 GENERAL CONSIDERATIONS

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium CDISC/Analysis Data Model (ADaM) standards. SAS v9.4 or higher software will be used to perform all data analyses (ADaM datasets, tables, figures, and listings).

Baseline will be defined as the most recent non-missing value prior to or on the same day of the first dose of glembatumumab vedotin. Generally, only pre-specified planned visits will be used in the by-visit summaries, statistical analyses and calculations of any derived safety parameters except for lab summary tables. All post baseline measurements including scheduled and unscheduled assessments will be used to derive the worst / best assessment for lab summary tables.

The primary response criterion is RECIST 1.1. Confirmation of response is required in defining best overall response (BOR) as the primary endpoint. The irRECIST is used as a secondary analysis for all efficacy endpoints except for OS.

All analyses specified in this plan will be performed by cohort. All baseline tables will include a column for each cohort and a column for overall. Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, Q1, Q3, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Unless otherwise stated, all listings will be sorted by cohort, subject number, and then by visit date if applicable.

5.1 Pooling of Centers

Data from all study centers will be pooled together for analyses in this study.

5.2 Multiplicity Adjustment

This is an early phase exploratory study and adjustment for multiplicity is not planned.

5.3 Subgroups

Subgroup analyses will be performed to explore the correlation between degree of gpNMB expression and anti-cancer activity of glembatumumab vedotin in advanced melanoma for efficacy endpoints. Rash developed in treatment cycle 1 will also be explored as another subgroup variable. Specifically, the following subgroup analyses will be performed for ORR, PFS and OS:

- Age group (<65, >=65)
- Gender (Female, Male)
- CNS involvement (Yes, No)
- Number of disease site (<=3, >3)
- ECOG PS (0, 1)
- GpNMB Expression (<95%, >=95%)
- Rash in cycle 1 (Yes, No). The medical term of rash is to be defined by medical manual review and documented prior to analysis. Only treatment-related rash is considered. If a subject only has 1 cycle of treatment, rash onset within 21 days from the first dose will be considered as rash in cycle 1.
- Time between last prior CPI and initiation of study treatment (<=3 months, >3 months).
- Duration of last prior CPI (<=3 months, >3 months).

- Cohort 3 only: PD-L1, positive (positive in >=1% tumor cells) vs negative

5.4 Adjustments for Covariates

No analysis adjusting for covariates are planned for this study.

5.5 Handling of Missing Data

Partially missing date of diagnosis needs to be imputed for calculating time from diagnosis to baseline. The following imputation rules will be applied:

- If only day is missing, impute as the first day of the month.
- If both day and month are missing, impute as Jan 1st.
- If year is missing, no imputation will be performed.

The above rules also apply to other diagnosis dates including date of metastatic disease, date of advanced disease, date of cancer surgery, radiation and prior cancer medications.

For partially missing additional cancer therapy date, the imputation is same as above except when only day is missing and the month is the same as in on-study progression date, in which case the day of additional cancer therapy will be imputed as the day of progression + 1 to avoid censoring a progression event due to an uncertain anticancer therapy start date.

For partially missing AE start dates (missing day and/or month), the following imputation rules will be applied:

- If both day and month of the AE start date are missing, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of the first dose given the AE end date is not prior to first dose. Otherwise, the month and day is imputed as the first day of the year (Jan 1st).
- If only day is missing, and if the year and month are equal to the first dose date, the AE start date will be imputed as the first dose date given the AE end date is not prior to first dose. Otherwise, the day will be imputed as "01". As a general consideration, imputed AE start date cannot be after AE end date if available.

6 STUDY SUBJECTS

6.1 Disposition and Withdrawals

Subject disposition will be summarized by treatment cohort based on Safety Population. Disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were treated, subjects who discontinued treatment, subject survival status, and subjects who discontinued from the study, with percentages based on the relevant cohort.

The reasons for study discontinuation and treatment discontinuation will also be summarized.

Subject disposition data will be presented in a data listing.

6.2 Protocol Deviations

The important protocol deviations and the Per Protocol (PP) population will be determined prior to the database lock. Protocol deviations will be listed by treatment cohort, patient number, and categorized according to the deviation reasons. All important protocol deviations will also be presented in a data listing.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Unless specified otherwise, the baseline values will be those values measured closest to but not after the first dose of study treatment.

A summary of demographics and baseline information will be presented by study cohort. Continuous data will be summarized using number, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using number and percentage of subjects in each treatment cohort. Percentages will be based on the total number of subjects in the Safety Population.

Subject demographic and baseline characteristics will also be presented in a listing.

7.1 Demographics

The following demographic variables will be summarized:

- Age (years)
- Age category (<=18, 19 - 64, >=65)
- Sex (male or female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)
- Baseline ECOG performance status (0, 1)

7.2 Disease Characteristics

The following baseline disease characteristics will be summarized:

- Time since initial diagnosis (years)
- Stage at initial diagnosis
- Stage at study entry
- Metastasis staging at study entry
- Histopathologic Type
- Mutations (BRAF, BRAF types and other mutations)
- Number of organs (disease sites) involved
- Most frequent disease site
- Historical or current CNS involvement
- Time since advanced and/or metastatic disease (calculated relative to first dose date)
- Number of Subjects with at Least One Additional Relapse or Disease Progression

- Tumor burden as measured by sum of diameter
- Elevated Lactate Dehydrogenase (LDH) (Yes, No)
- Cohort 3 only: PD-L1, positive (positive in >=1% tumor cells) vs negative
- % positive gpNMB in epithelial cells (descriptive statistics and categories: 100% vs <100%)

7.3 Prior Therapy and Medical History

Prior medical and surgical history will be coded by MedDRA (Medical Dictionary for Regulatory Activities) and will be summarized by treatment cohorts.

The following prior anti-cancer treatment parameters will be summarized:

- Number of prior systemic anti-cancer regimens
- Prior cancer treatment class: check point inhibitor (CPI) with subcategories including CTLA-4 and PD-1/PD-L1, other immunotherapy, BRAF related TKI, cytokines and cytotoxic-containing therapy
- Number of prior CPI containing regimens
- Best response to first prior CPI treatment
- Best response to and duration of last prior CPI treatment
- Surgery/Biopsy description (Resection, Biopsy or Other)
- Prior radiation therapy (Yes or No)
- Prior cancer surgeries (Yes or No, biopsy excluded)
- Time from last anti-cancer therapy to first dose of glembatumumab vedotin (≤ 2 or >2 months)
- Time from CPI as last anti-cancer therapy to first dose of glembatumumab vedotin (≤ 2 months, >2 month to ≤6 months, or >6 months)

7.4 Prior and Concomitant Medications

All medications will be documented on the case report form (CRF) if taken within 28 days prior to the first dose of study treatment through (whichever occurs first) either a) 28 days after the last dose of study treatment, or b) initiation of alternate anticancer therapy. In addition, all anticancer therapies should be recorded throughout the duration of study follow-up.

All medications will be coded using the World Health Organization (WHO) drug dictionary. Prior medications are defined as medications that received before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing into the treatment period, or (2) started on or after the date of the first dose of study drug up to 28 days after last dose.

The number (%) of subjects who took prior and concomitant medications will be summarized on the anatomical class (ATC) and preferred term (PT) by dose cohorts. A summary of concomitant anti-cancer therapies will be summarized separately by PT.

8 EFFICACY ANALYSES

8.1 Analyses of the Primary Endpoint

The primary endpoint is objective response rate (ORR). ORR will be estimated based on the proportion of evaluable subjects who achieve best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST 1.1 that are confirmed at an interval of at least 28 days. The estimate of the objective response rate will be accompanied by one-sided and two-sided 95% Clopper-Pearson confidence intervals. For Cohort 1, a one-sample exact binomial test with one-sided significance level of 0.05 will be used to test the response rate under the null (H_0: ORR=5%) and alternative (H_a: ORR=15%) hypotheses (5% vs. 15%, respectively). For each of Cohorts 2 and 3, the estimate of ORR will be compared with the fixed rates of 5% and 10% with one-sided significance level of 0.10. The primary ORR analysis is based on evaluable population and secondarily on Safety Population. The analysis of ORR will also be summarized for the PP population.

In this study, a minimum interval of 5 weeks from first dose date is required for stable disease (SD) status. Subjects with Not Evaluable (NE) or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating ORR).

Secondary analyses of ORR will include responses observed at a single time point (i.e., analysis of ORR will be summarized based on confirmed and unconfirmed CR or PR) based on Safety Population.

Waterfall plots will be used to depict graphically the maximum percent decrease from baseline in the sum of longest diameters of target lesions. A spider plot will be generated to depict changes in the sum of longest diameters of target lesions over time. A swimmer plot will also be used to show the effect of study treatment on tumor response for individual subjects.

Tumor assessment data after initiation of other anticancer therapy will be excluded for response related efficacy endpoints including BOR, DOR, PFS, waterfall plot, spider plot and swimmer plot.

For Cohorts 2 and 3, supplementary analyses of tumor response and progression will be performed using irRECIST criteria (in which new lesions do not necessarily constitute progression, but contribute to the calculated sum of diameter of all measurable disease). To be noted, if not all target lesions are measured at a visit, the sum of diameters should not be calculated.

As a secondary exploratory analysis, BOR and ORR by irRECIST criteria will be derived and summarized in a similar fashion as in the primary analyses. Specifically, for Cohorts 2 and 3, ORR will be compared with reference levels of 5% and 10%. One-sample exact binomial test with one-sided significance level will be provided for each test. Waterfall plots, spider plots and swimmer plots will be used to depict graphically the maximum percent decrease from baseline , changes in tumor burden (sum of longest diameters of target lesions and new lesions) over time and the effect of study treatment on tumor response, by irRECIST criteria for individual subjects.

8.2 Analyses of Secondary Endpoints

8.2.1 PFS

Progression Free Survival (PFS) is defined as the time from the study treatment first dose to the earlier of disease progression or death due to any cause. Disease progression will be assessed using RECIST 1.1. The progression and censoring dates will be based on the May 2007 FDA Guidance for Industry, '*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*'. Determination rules for events or censored PFS is summarized in Table 2.

Table 2: Date of Event or Censoring for the Primary PFS analysis

Situation	Date of Event or Censoring	Outcome
Disease progression between scheduled disease assessments	Date of progression	Event
Death between scheduled disease assessment	Date of death	Event
Death before the first planned disease assessment at 6 weeks (plus 1 week window) without any disease assessment	Date of death	Event
No baseline disease assessments	Date of first dose	Censored
No post-baseline disease assessments without death before the first planned disease assessment	Date of first dose	Censored
Discontinuation of study treatment without progression (i.e., due to toxicity, withdrew consent, or lost to follow-up) and no further radiographic assessment[a]	Date of last radiological assessment	Censored
Alternate anticancer treatment started without documentation of disease progression beforehand[b]	Date of last radiological assessment prior to start of further anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments[c]	Date of last radiological assessment without documented progression disease prior to death/progression	Censored
Patients who have not progressed and are alive	Date of last radiological assessment without documented progression disease	Censored

a. For a patient who discontinues study treatment without PD and continues to have radiographic assessments, post-treatment radiographic assessments will be considered for PFS analyses according to the rules in this table.

b. Alternate anticancer treatment interventions that are diagnostic (e.g. biopsy) or palliative (e.g., local radiation for painful nodule), as determined by medical review, will not routinely require censoring unless they are determined to interfere with the assessment of the patients' disease status.

c. Disease assessments are planned every 6 (±1) weeks for the first 6 months (24 weeks); and every 9 (±2) weeks, thereafter, until disease progression. The interval of two missed scheduled assessments is calculated according to the

Situation	Date of Event or Censoring	Outcome
scheduled assessment frequency and the corresponding window (1 or 2 weeks depending on assessments scheduled before or after 6 months).		

PFS will be summarized descriptively using the Kaplan-Meier method. Median PFS and its corresponding 95% confidence interval will be reported. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% confidence interval.

The PFS rate and its corresponding 95% confidence interval for various landmark time points (i.e., 6 months and 1 year) will also be estimated using the Kaplan-Meier method. The Kaplan-Meier curve of PFS will be provided.

Subgroup analyses for PFS will be performed, Kaplan-Meier curves and a forest plot will be presented.

8.2.2 Duration of response (DOR) and disease control rate (DCR)

Duration of Response (DOR) will be calculated for subjects who achieve confirmed CR or PR. For such subjects, DOR is defined as the time from response criteria are first met for either CR or PR, until the first date PD is objectively documented, or until death. DOR will be right-censored based on the same rules as described for PFS above.

DOR will be summarized descriptively and the median DOR will be estimated using the Kaplan-Meier method.

Swimmer plots will be provided depicting graphically the duration of response for patients who achieve complete response or partial response per RECIST 1.1 in each cohort. For Cohorts 2 and 3, swimmer plots of tumor response will also be provided per irRECIST criteria.

Disease control rate (DCR) is defined as the proportion of evaluable subjects who achieved BOR of CR or PR with any duration or SD with duration of at least 3 months (i.e., >=3 months). The estimate of the DCR will be accompanied by one-sided and two-sided 95% Clopper-Pearson confidence intervals. Additionally, DOR and DCR will be derived and summarized based on the irRECIST criteria for Cohorts 2 and 3 subjects.

8.2.3 Overall Survival (OS)

Overall survival (OS) is defined as the time from first dose to death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be censored at the last known alive date.

The OS will be summarized descriptively using the Kaplan-Meier method; median OS and its corresponding 95% confidence interval will be reported. Median follow-up for OS will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996). Kaplan-Meier curve of OS will be provided.

8.3 Exploratory Analysis

GpNMB expression will be summarized over time and/or by specific prior therapies.

If feasible, based on the range of gpNMB expression, the correlation between gpNMB expression level and maximum percent decrease from baseline in the sum of longest diameters of target lesions will be evaluated using linear regression. Transformation might be necessary if

data distribution is not normal. For this analysis, all subjects will be used, with gpNMB expression measured on a continuous scale (percentage of gpNMB-positive tumor cells). To examine the predictive power of various cut-off values for gpNMB expression, a receiver operating curve (ROC) analysis for response data (Gönen and SAS Institute. 2007) will be performed.

The correlation between gpNMB expression levels and efficacy endpoints including ORR, PFS, and OS will be explored using subgroup analyses by gpNMB level categories. Descriptive statistical tests may be used to compare the efficacy endpoint in subjects with different gpNMB level categories, if appropriate. Cox proportional hazard model may also be used to assess the gpNMB effects on PFS and OS by considering gpNMB expression in a continuous and/or categorical scale.

For the above analyses, the most recent tumor sample will be utilized to determine the tumor gpNMB expression level for each patient. Additional exploratory analyses may be performed to examine the distribution and intensity of gpNMB expression (i.e., staining intensity and percentage of positive tumor and stromal cells) relative to outcome, as well as comparison of Historic and Pre-Study samples to determine whether gpNMB expression changes over time and/or with specific prior therapies.

ORR, PFS and OS will be summarized by whether patients experienced rash in cycle 1 which is defined in Section 5.3. A by-subject listing will be provided for gpNMB expression data and related efficacy endpoints.

Gene signature from skinfold biopsy samples for cohorts 2 and 3 patients will be analyzed for its correlations with rash in cycle 1 and with ORR and PFS.

9 SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the safety population by cohort.

9.1 Extent of Exposure

The duration of exposure to study treatment, total number of doses and cumulative dose administered will be summarized for each treatment within each cohort. Relative dose intensity will be additionally calculated for Glembatumumab exposure. The individual dose is calculated using the actual body weight of the patient at baseline, and the dose may remain constant throughout the study unless a greater than 10% change in weight is observed, in which case the weight at the cycle will be used.

The calculations for the above statistics for each treatment in each cohort are as follows:

- Duration of Exposure (days) = Date of Last Dose – Date of First Dose + 1
- Total number of doses= the total number of doses with volume added to bag>0 and total volume infused>0
- The actual dose at each cycle (mg/kg) =
    - **Glembatumumab**: Total Volume infused (mL) / [Volume of Infusion bag (mL)] * Volume of Glembatumumab Vedotin added to bag (mL) * 5 (mg/mL) / weight (kg)
    - **Varlilumab**: Total Volume infused (mL) / [Total volume prepared (mL)] * Volume of Varlilumab added to bag (mL) * 5 (mg/mL) / weight (kg)

  - **Nivolumab:** Total Volume infused (mL) / [Total volume prepared (mL)] * Volume of Nivolumab added to bag (mL) * 10 (mg/mL) / weight (kg)
  - **Pembrolizumab:** Total Volume infused (mL) / [Total volume prepared (mL)] * Volume of Pembrolizumab added to bag (mL) * 25 (mg/mL) / weight (kg)
- Cumulative dose for each treatment is the sum of all actual doses for all cycles in mg/kg
- For Glembatumumab, Relative Dose Intensity = Actual Dose Intensity (ADI) / Planned Dose Intensity (PDI), where ADI (mg/kg/3 weeks) = Cumulative Dose (mg/kg) / ((Date of Last Dose – Date of First Dose + 21) / 21) and PDI (mg/kg/3 weeks) = 1.9 mg/kg/3 weeks.

9.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities Terminology (using latest MedDRA version). All AEs will be presented in a by-subject listing. Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes or abnormalities in the subject's physical examination, vision examination, vital signs, ECG, and clinical laboratory results.
These analyses will be performed using the safety population by cohort.

9.2.1 Treatment emergent AE

Treatment emergent AEs (TEAEs) include all AEs that occurred or increased in severity from first dose of study treatment up to 28 calendar days after the last administration of glembatumumab vedotin or 70 calendar days after the last administration of varlilumab (whichever occurs later, Cohort 2); 70 days after last dose of the PD-1 targeted checkpoint inhibitor (whichever occurs later in Cohort 3). In addition, if an AE cannot be determined as treatment-emergent or not due to incomplete/missing data, conservatively, it will be considered as treatment emergent and included in the summary tables. Any AE summary tables described in this plan are based on treatment-emergent AEs unless specified otherwise. The number and percentage of subjects experiencing at least one treatment emergent adverse event will be tabulated by MedDRA primary system organ class, preferred term and cohort. For the number of subjects with AEs, subjects reporting the same event more than once will have that event counted only once within each body system, and once within each preferred term.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Related". A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study treatment as "Related". The number and percentage of subjects experiencing at least one treatment emergent AE considered related to treatment will also be summarized.

TEAEs will also be summarized by NCI-CTCAE version 4.0 grade. Again, multiple occurrences of the same event are counted once per subject using the maximum severity. If the grade of an AE is missing, the event will be included in the total column for the corresponding cohort. TEAEs with actions of study treatment delayed/interrupted, reduced, or discontinued will be summarized in by CTCAE grade. Summary statistics of the number and percentage of subjects experiencing at least one treatment emergent AE by study visit will be presented as well. The subject incidence count for each visit will be from the time of the pervious visit, except the baseline visit, where it counts from the time of first dose.

9.2.2 Serious Adverse Events

The number and percentage of subjects experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class and preferred term for each cohort.
In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

9.2.3 AE with outcome of death

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status). The primary cause of death will also be summarized.

9.2.4 Grouped AE

Grouped AEs including Anemia, Neutropenia, Thrombocytopenia, Leukopenia, Neuropathy and Rash will be determined by medical review of the AEs, and will be summarized in the AE tables in a similar fashion as AE preferred terms.

9.3 Laboratory Parameters

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.
If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.
The actual values in clinical laboratory parameters will be summarized at baseline and over time on study by treatment group; summary statistics for change from baseline of hematology, clinical chemistry, and urinalysis values will also be presented.

9.3.1 Hematology and Clinical Chemistry

The descriptive summary table with actual lab values and change from baseline values will be generated based on protocol defined hematology parameters (i.e., Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Erythrocyte count (RBC), Leukocytes (WBC), Platelets, Neutrophils, Lymphocytes, Monocytes, and Eosinophils) and chemistry parameters (i.e., Sodium, Potassium, Chloride, Bicarbonate, Glucose (nonfasting), Blood urea nitrogen (BUN), Creatinine, Calcium, Phosphate, Alkaline phosphatase, Alanine transaminase/ Serum Glutamic Pyruvate Transaminase (ALT/SGPT), Aspartate transaminase/ Serum Glutamic Oxaloacetic Transaminase (AST/SGOT),Total protein, Albumin, Lactate Dehydrogenase (LDH), Total Bilirubin). For hematology and chemistry parameters, shift tables of the change in NCI CTCAE grade from baseline to the post-baseline by visit and worst CTCAE grade will be generated. The number and proportion of patients with directional shifts above or below the standard normal range will be summarized for selected laboratory tests.

By-subject listings of hematology and chemistry data will be presented. Laboratory values outside of normal limits will be identified in data listings and will be flagged for high and low values.

9.3.2 Urinalysis

A by-subject listing of Urinalysis data will be presented. The parameters to be listed include: pH, protein, glucose, blood, specific gravity, microscopic evaluations (available only if urinary infection is clinically indicated). For cohort 2, thyroid function test parameters including TSH, free T4 and T3 will be listed additionally.

9.4 Vital Signs

The actual values of vital sign parameters including temperature (Celsius), pulse rate (beats/min), respiration rate (breaths/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and weight (kg) will be summarized over time. Changes from baseline will also be presented. A by-subject listing for vital sign data will also be presented according to eCRFs.

9.5 Electrocardiograms

Electrocardiogram (ECG) assessments are planned at Screening, Day 1 of Cycle 1, and End of Treatment visit. ECG results will be summarized using shifts from baseline for the number and percentage of subjects with abnormal (clinically significant and not clinically significant, separately) and normal findings, as reported by the local investigator.

A by-subject listing for ECG data will also be presented according to eCRFs.

9.6 ECOG PS

Eastern Cooperative Oncology Group (ECOG) performance status will be evaluated at Screening, Day 1 of each treatment cycle, and End of Treatment visit. ECOG performance status will be summarized at baseline and each post baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. In addition, post-baseline scores will be summarized descriptively using shifts from baseline.

A by-subject listing for ECOG data will also be presented according to eCRFs.

10 PHARMACOKINETIC, PHARMACODYNAMIC AND IMMUNOGENICITY ANALYSES

All planned analyses for PK, PD and immunogenicity will be provided in a separate report. Data listings and/or basic descriptive summaries may be presented in the Clinical Study Report.

11 INTERIM ANALYSES

No interim analysis is planned.

12 CHANGES FROM THE PLANNED ANALYSES

In the protocol, ITT population and Safety population are equivalent. For simplicity of reporting, the term of *ITT Population* is retired.

13 SOFTWARE

14 TABLES, LISTINGS, AND GRAPHS (TLGS) SHELLS AND PROGRAMMING SPECIFICATIONS

15 REFERENCES

Eisenhauer, E. A., P. Therasse, et al. (2009). "New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1)." Eur J Cancer **45**(2): 228-247.

Gönen, M. and SAS Institute. (2007). Analyzing receiver operating characteristic curves with SAS. Cary, NC, SAS Pub.

Nishino, M., A. Giobbie-Hurder, et al. (2013). "Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements." Clin Cancer Res **19**(14): 3936-3943.

16 APPENDICES

16.1 Schedule of Assessment

Visit	Screening[2]	Treatment Visits[3]					
		Cycle 1/ Day 1	Cycle 1/ Day 7 (Cohorts 2 and 3)	Cycle 1/ Day 14 (Cohorts 2 and 3)	Cycle 2/ Day 1	Cycle 3, 4, 5, etc./ Day 1	End of Treatment[4]
Visit window[1]	*Day -28 to Day -1*		*+/- 1 day*	*+/- 1 day*	*+/-3 days*	*+/-3 days*	*Within 28 days post-dosing*
Informed Consent, and, if applicable, HIPAA	X						
Tumor tissue[7]	X[8]	X[9]					
Skin fold biopsy[7]	X[8]						
Medical history[10]	X	X					
Physical examination[11]	X	X[12]			X	X	X
Vital signs[13]	X	X			X	X	X
ECOG performance status	X	X[12]			X	X	X
Electrocardiogram (ECG)	X						X
Pregnancy test[14]	X	X[12]					
Hematology[15]	X	X[12]	X	X	X	X	X
Blood chemistry[15]	X	X[12]	X	X	X	X	X
Urinalysis/dipstick[15]	X	X[12]					X
Thyroid function test (Cohort 2)[15]	X	X[12]				X (Odd cycles)	X
Immunogenicity[16, 17]		X				X (Odd cycles)	X
PBMC collection[17, 18]		X			X	X (Cohorts 2 and 3, Cycle 5 only)	
PK sample collection[17, 19]		X			X	X (Odd cycles)	X
PD sample collection[17]		X			X		X
Disease assessment[20]	X						
Administration of glembatumumab vedotin[21]		X			X	X	
Administration of varlilumab[22] (Cohort 2)		X			X	X[21]	
Administration of PD-1 targeted CPI (Cohort 3)[23]		X	X[23]				
Survival status							
Concomitant medication review[24]	X	X	X	X	X	X	X
Adverse event monitoring[25]		X	X[26]	X[26]	X	X	X

1. 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.
2. Unless otherwise specified, all study assessments should be performed prior to administration of study treatment(s), and may be performed up to 24 hours prior to treatment administration if assessments remain within the specified visit window.

3. In Cohort 2, varlilumab and glembatumumab vedotin will be administered as separate infusions with a break of at least 30 minutes between infusions. Varlilumab should be infused over 90 (±10) minutes and administered before glembatumumab vedotin, also infused over 90 (±10) minutes. Varlilumab will be administered on Day 1 of Cycles 1, 2, 4, 6, 8, and 10 only. Patients in Cohort 1 should be monitored for at least 1 hour following the last administration of study drug to monitor for infusion reaction/cytokine release syndrome/hypersensitivity reaction. Patients in Cohort 2 should be observed on Cycle 1 Day 1 for at least 2 hours after the last study drug, and for at least 1 hour at all subsequent dosing visits. Infusions should be given in a monitored setting that has ready access to an intensive care unit in case of a severe infusion reaction
4. Administration of the PD-1 targeted CPI should be continuous from the prior standard of care treatment regimen during which the most recent disease progression occurred. No more than 1 dose of a PD-1 targeted CPI should be missed between the most recent disease progression and initiation of treatment on study. Day 1 of Cycle 1 occurs with the first dose of glembatumumab vedotin which is administered on the same day as the PD-1 targeted CPI. When both glembatumumab vedotin and the PD-1 targeted CPI are administered on the same day, the drugs will be administered as separate infusions. The PD-1 targeted CPI should be the first infusion and glembatumumab vedotin administered at least 30 minutes later as the second infusion. Patients in Cohort 3 should be observed on Cycle 1 Day 1 for at least 2 hours after the last study drug, and for at least 1 hour at all subsequent dosing visits. Infusions should be given in a monitored setting that has ready access to an intensive care unit in case of a severe infusion reaction. The PD-1 targeted CPI will be administered in combination with glembatumumab vedotin until disease progression (using study screening disease assessment as baseline reference) or intolerance.
5. Additional clinic visits and monitoring (such as laboratory assessments) relevant to the administration of the PD-1 targeted CPI will be conducted in accordance with standard of care when appropriate. However, all CPI dosing and adverse events occurring between study visits will be documented in the eCRF.
6. All concomitant medication will be documented in the Case Report Form (CRF) 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 should be recorded throughout the duration of study follow-up.
7. For patients who develop grade 3 treatment-related rash and who provide appropriate consent, punch biopsies and photographs of the rash, as well as uninvolved skin, are strongly encouraged. Samples may be analyzed centrally; in these cases, collection, processing and shipping instructions will be provided separately.
8. Adverse event monitoring on Cycle 1 Day 7 and Cycle 1 Day 14 for patients in Cohorts 2 and 3 can be performed in person or by telephone to determine if the patient is experiencing any adverse events.
9. Events occurring >28 days after discontinuation of glembatumumab vedotin, >70 days after discontinuation of varlilumab (Cohort 2), or >70 days after discontinuation of the PD-1 targeted CPI (Cohort 3) are only reportable if both serious (SAE) and potentially treatment-related.
10. A delay in study treatment or performance of study visits due to holidays, weekends, inclement weather or other unforeseen circumstances will be permitted and not considered a protocol violation. However, significant delays (i.e., greater than one week) due to these reasons should be discussed with the study medical monitor to reach consensus on subsequent scheduling. See (Protocol Section 8.5) and (Protocol Section 8.7) for management of dosing delays due to toxicity.
11. Informed consent may be signed at any time prior to or during the screening period. No study-specific 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.
12. Patients will receive study treatment until intolerance, progression of disease, or any of the other criteria for discontinuation of study treatment (Protocol Section 7.2.4.1.1) are met. All cohorts will receive glembatumumab vedotin on a three-week cycle. Cohort 2 patients will also receive varlilumab on Day 1 of Cycles 1, 2, 4, 6, 8, and 10. Cohort 3 patients will also receive a PD-1 targeted CPI per institutional standard of care.
13. The End of Treatment Visit should be performed within 28 days after last dose of study treatment and prior to initiation of alternate therapies.
14. Disease assessments will be performed every 6 weeks (±1 week) for 6 months and every 9 weeks (±2 weeks) thereafter, scheduled based on the first dose of glembatumumab vedotin at C1D1, until documented progression of disease or initiation of alternate anticancer therapies. For Cohorts 2 and 3, in cases of apparent progression that may reflect enhanced inflammation and/or an initial imbalance in the kinetics of tumor growth and anti-cancer immune activity, continued combination treatment may be allowed with permission granted from the Celldex Medical Monitor, until a second radiologic confirmation of progression performed at the next scheduled disease assessment (or sooner if clinically indicated) (Protocol Section 5.5.3 and Protocol Section 7.2.4.1.1). If a partial or complete response is noted, a follow-up disease 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 may continue to receive study treatment until remaining lesions meet criteria for progression of disease.

15. Subsequent to disease progression, all patients 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. These visits may be performed by telephone.
16. Assessment of gpNMB expression will be performed by IHC, retrospectively, at a central laboratory on FFPE Historic and Pre-entry (tumor and skin fold [axilla or groin] biopsy) samples. Skin biopsy should be 3-5 mm in diameter. Additional analyses performed centrally may also include, but are not limited to, 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, biomarkers related to immune activation and localization of glembatumumab vedotin, CR011, or MMAE at the tumor site in post-treatment samples. Sample collection, processing and shipping instructions will be provided separately.
17. Historic FFPE samples must represent the advanced stage of disease (Stage III or IV). Pre-entry FFPE samples must be obtained within 12 weeks prior to study entry, be subsequent to the last systemic anticancer therapy received, and be post-tumor progression. For patients who must undergo biopsy to obtain a FFPE Pre-entry sample, biopsy sites must be soft tissue tumor or visceral lesions that can be biopsied with acceptable clinical risk (as judged by the investigator). The biopsy site chosen should not have been previously irradiated and must be distinct from RECIST 1.1 target lesions. Tissue from multiple previous collection dates should also be submitted, when available/feasible, in order to further understand how gpNMB levels may change over time and/or with cancer stage. Skin biopsies (Cohort 2) must be obtained within 12 weeks of study entry.
18. At recurrence, biopsy and central analysis of recurrent tumor is optional but strongly encouraged. Similarly, in the event of tumor resection or biopsy performed per standard of care anytime during treatment or following tumor progression, submission of these tissue samples for central analysis is strongly encouraged.
19. Medical history includes demography, melanoma history, previous surgeries/therapy, and pre-existing diseases. At Cycle 1, Day 1, medical history is updated prior to administration of study drug.
20. Complete physical exam should be performed at screening; thereafter, symptom-directed exams are acceptable.
21. Assessments do not need to be repeated if completed within the previous 24 hours as part of the screening assessment.
22. Vital signs to include height (at screening only), weight, respiration, pulse, temperature, and resting systolic and diastolic blood pressure. In Cohort 2 on glembatumumab vedotin and varlilumab dosing days, vital signs should be assessed pre-infusion, at 45 (±15) minutes during each infusion, and within one- half hour following completion of each infusion. In Cohort 3, vital signs should be assessed for each glembatumumab vedotin infusion as follows: pre-infusion, at 45 (±15) minutes during the infusion, and within one-half hour following completion of the glembatumumab vedotin infusion. Additionally, when the PD- 1 targeted CPI is administered with or without glembatumumab vedotin dosing, vital signs should be assessed prior to each PD-1 targeted CPI infusion and additionally, as necessary, per clinical and institutional standards. (Note: weight is only assessed once per visit.)
23. Serum or urine pregnancy test only for women of childbearing potential. Patients of non-childbearing potential include those who are ≥60 years, surgically sterilized, or postmenopausal 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 FSH and/or estradiol) are available to ensure postmenopausal status.
24. Laboratory assessments must include the following, when indicated. Hematology results must be reviewed prior to dosing. For patients in Cohort 2, liver function tests (i.e., ALT, AST, and total bilirubin) and creatinine must also be reviewed prior to dosing. In addition, in Cohort 2, thyroid function tests must be performed at screening, at Cycle 1, at every odd cycle (i.e., Cycles 3, 5, 7, etc.), and at End of Treatment.

	Clinical Chemistry:	**Urinalysis**
n	Sodium	pH
	Potassium	Protein
uscular volume (MCV)	Chloride	Glucose
e count (RBC)	Bicarbonate	Specific gravity
(WBC)	Glucose (nonfasting)	Blood
	Blood urea nitrogen (BUN)	
l:	Creatinine Calcium	*Microscopic examination must be performed at*
s	Phosphate	*baseline and, if clinically indicated, at subsequent visits*
es	Alkaline phosphatase	*(if urinary infection is suspected then a negative urine*
	Alanine transaminase (ALT/SGPT) Aspartate	*culture is required prior to enrollment.)*
s	transaminase (AST/SGOT) Total protein	
	Albumin	**Thyroid Function Test (Cohort 2 only)**
l should be reported consistently	Lactate Dehydrogenase (LDH)	TSH
the study as either an absolute	Total Bilirubin	Free T4 and T3
ferred) or as a percentage.		*Free T4 and free T3 performed at screening, and then*
		only if TSH is abnormal at subsequent visits.

25. Samples for immunogenicity will be collected prior to dosing on Day 1 of "odd" cycles (i.e., Cycles 1, 3, 5, 7, etc.).
26. Analyses will be performed centrally. Sample collection, processing and shipping instructions will be provided separately.
27. For Peripheral Blood Mononuclear Cell (PBMC) collection on Cycle 1/Day 1 and Cycle 2/Day 1, samples are collected prior to dosing. For Cohort 1 an additional sample is collected at End of Treatment. For Cohort 2s and 3 an additional

sample is collected on Cycle 5/Day 1 prior to dosing. 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. Additional analysis may include response assessment to potentially relevant tumor antigens and analysis of myeloid derived suppressor cells. Details on sample collection and handling will be provided separately. PBMC samples will be collected until such time Celldex informs the sites that further data is not needed.

28. Cohort 1: On Day 1 of Cycle 1 and 2 only, glembatumumab vedotin PK samples will be collected prior to dosing and at end of infusion (at or within 30 minutes after completion of infusion). A PK sample will also be collected at the End of Treatment visits.
29. Cohort 2: On Day 1 of Cycles 1, 2, and 5, a total of three PK samples will be collected on each day for glembatumumab vedotin and varlilumab PK analysis. PK samples will be collected prior to dosing of varlilumab, at end of varlilumab infusion (at or within 10 minutes after completion of infusion), and at end of glembatumumab vedotin infusion (at or within 10 minutes after completion of infusion). On Day 1 of Cycles 3, 7, and subsequent odd cycles, only one PK sample will be collected prior to the first infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction. A PK sample will also be collected at the End of Treatment visits.
30. Cohort 3: On Day 1 of Cycles 1, 2, and 5, a total of two PK samples will be collected on each day for glembatumumab vedotin PK analysis. PK samples will be collected prior to dosing of glembatumumab vedotin and at end of infusion (at or within 10 minutes after completion of infusion). On Day 1 of Cycles 3, 7, and subsequent odd cycles, only one PK sample will be collected prior to the first infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction. A PK sample will also be collected at the End of Treatment visits.
31. For Cohorts 1, 2, and 3, analysis may also include circulating soluble gpNMB levels or other soluble molecules.