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

Sponsored by: Celldex Therapeutics, Inc.

[redacted]

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This study is to be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with ICH guidelines on Good Clinical Practice and regulatory requirements, as applicable.

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1. STUDY PERSONNEL AND STUDY ADMINISTRATION

Prior to the initiation of the study, Celldex (or its designee) will provide a study roster with contact information for applicable study personnel.

Note: As used throughout this document, "Celldex" refers to Celldex or any designee to whom study-related responsibilities have been appropriately delegated.

2. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADC	Antibody-Drug Conjugate
AE	Adverse Event
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)
AT	Aminotransferase
BLC1	B-Cell Leukemia Line
CI	Confidence Interval
CITN	Cancer Immunotherapy Trials Network
CPI	Checkpoint Inhibitor
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA	Cytotoxic T-Lymphocyte Antigen 4
CYP450	Cytochrome P450
DC	Dendritic Cell
DCTD	Division of Cancer Treatment and Diagnosis
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
ERK	Extracellular-Signal-Regulated Kinases
FFPE	Formalin fixed and Paraffin-Embedded
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
gpNMB	Glycoprotein NMB
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
IC	Investigator's Choice
ICH	International Conference on Harmonization
IgG2	Immunoglobulin G, Subclass 2
IHC	Immunohistochemistry
IND	Investigational New Drug
irAE	Immune-related Adverse Event
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee

Abbreviation	Definition
irRECIST	Immune-related Response Evaluation Criteria for Solid Tumors
ITT	Intention to Treat
i.v.	Intravenous
Kg	Kilogram
LCMS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
M-CSF	Macrophage Colony Stimulating Factor
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliters
MMAE	Monomethyl auristatin E
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (of the United States)
NCIC	National Cancer Institute of Canada
NE	Not evaluable
NIH	National Institutes of Health
NK	Natural Killer
NR	Not Reported
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed cell death
PD-L1	Programmed death-ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetics
poly-ICLC	Polyinosinic-polycytidylic acid double-stranded RNA, poly-L-lysine, and carboxymethylcellulose (a TLR3 agonist)
PP	Per-protocol
PR	Partial Response
qw	Every week
q2/3w	Two of three weeks
q3w	Every three weeks
RBC	Erythrocyte Count
RECIST	Response Evaluation Criteria for Solid Tumors
ROC	Receiver Operating Characteristic Curve
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SCF	Stem Cell Factor
SD	Stable Disease
SOPs	Standard Operating Procedures

Abbreviation	Definition
TA	Total Antibody
TBL	Total Bilirubin
TLT	Treatment-Limiting Toxicity
ULN	Upper Limit of Normal
vc	Valine-Citrulline
WBC	White blood count

3. PROTOCOL SYNOPSIS

Protocol number:	CDX011-05
Title:	A Phase II study of glembatumumab vedotin, an anti-gpNMB antibody-drug conjugate, as monotherapy or in combination with immunotherapy in patients with advanced melanoma
Investigational Treatment:	Glembatumumab vedotin (CDX-011; CR011-vcMMAE): a fully-human IgG_2 monoclonal antibody (CR011) against glycoprotein NMB (gpNMB) coupled to monomethyl auristatin E (MMAE) via a protease-sensitive valine-citrulline peptide linker Varlilumab (CDX-1127): a fully human IgG_1 agonist anti-CD27 monoclonal antibody (mAb)
Additional Therapies:	Nivolumab (Opdivo®): A fully human IgG_4 mAb against programmed cell death 1 (PD-1) Pembrolizumab (Keytruda®): A humanized IgG_4 mAb against PD-1 CDX-301: Recombinant Human Flt3 Ligand (rhuFlt3L)
Indication:	Patients with unresectable Stage III or Stage IV melanoma who have progressed through or after standard therapies
Number of Patients:	Approximately 160 patients will be enrolled: approximately 60 patients will be enrolled in the glembatumumab vedotin monotherapy (Cohort 1), approximately 30 patients will be enrolled in the glembatumumab vedotin and varlilumab combination (Cohort 2), approximately 30 patients will be enrolled in the glembatumumab vedotin and a PD-1 targeted CPI combination (Cohort 3), approximately 10-12 patients will be enrolled in the glembatumumab vedotin and CDX-301 combination (Cohort 4) and, depending on a review of the safety and activity of the previous cohorts, approximately 30 patients may subsequently be enrolled in the glembatumumab vedotin /CDX-301/PD-1 targeted CPI combination (Cohort 5).
Number of Study Centers:	Approximately 15 US study centers will participate.
Objectives:	<u>Primary</u> • To evaluate the anti-cancer activity of glembatumumab vedotin as monotherapy (Cohort 1), in combination with varlilumab (Cohort 2), in combination with a PD-1 targeted checkpoint inhibitor (CPI) (Cohort 3), or in combination with glembatumumab vedotin, CDX-301, and a PD-1 targeted CPI (Cohort 5) in advanced melanoma as measured by the objective response rate (ORR) per RECIST 1.1. To evaluate the safety and tolerability of the combination of glembatumumab vedotin and CDX-301 (Cohort 4). <u>Secondary</u> • To further assess the anti-cancer activity of glembatumumab vedotin as monotherapy, in combination with varlilumab, in combination with a PD-1 targeted CPI, or in combination with CDX-301 and a PD-1 targeted CPI in advanced melanoma, as assessed by progression-free survival (PFS), duration of response (DOR) and overall survival (OS). To assess the anti-cancer activity of the combination of glembatumumab vedotin and CDX-301 in advanced melanoma, as assessed by ORR, PFS, DOR, and OS.

	• To investigate if the anti-cancer activity of glembatumumab vedotin alone or in combination with immunotherapies 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 immunotherapies in advanced melanoma <u>Exploratory</u> • 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; analysis of peripheral blood subsets; to investigate the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations (Cohorts 4 and 5) • To further characterize the pharmacokinetics of glembatumumab vedotin, varlilumab, and CDX-301, and immunogenicity of glembatumumab vedotin, varlilumab, and CDX-301 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 in combination with immunotherapy as measured by the ORR and PFS per Immune-Related RECIST (irRECIST)
Overview of study design:	This is an open-label Phase II study of glembatumumab vedotin in patients with unresectable Stage III or IV melanoma who have previously received CPIs. This study consists of 5 cohorts. In Cohort 1, glembatumumab vedotin will be administered as monotherapy. In Cohort 2, glembatumumab vedotin will be combined with varlilumab. In Cohort 3, glembatumumab vedotin will be combined with a PD-1 targeted CPI, nivolumab or pembrolizumab. In this cohort, patients whose last treatment regimen included nivolumab or pembrolizumab, and per institutional standard of care would continue to receive a PD-1 targeted therapy despite progression, will receive either nivolumab or pembrolizumab in combination with glembatumumab vedotin, to determine whether the addition of glembatumumab vedotin can induce an effective anti-melanoma immune response and improved anti-cancer activity. Patients who previously received nivolumab in combination with ipilimumab and have discontinued ipilimumab would continue with nivolumab, or pembrolizumab, in combination with glembatumumab vedotin. Patients who experienced disease progression on nivolumab may receive nivolumab or pembrolizumab in combination with glembatumumab vedotin. Patients who experienced disease progression on pembrolizumab may receive nivolumab or pembrolizumab in combination with glembatumumab vedotin. In Cohort 4, glembatumumab vedotin will be combined with CDX-301 to determine the safety and tolerability of the combination and to investigate the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations. If glembatumumab vedotin can be administered safely in combination with CDX-301 (Cohort 4) and with a PD-1 targeted CPI (Cohort 3), then Cohort 5 will evaluate whether the anti-tumor immune responses would likely be further augmented by combining all three agents in patients who have previously failed a CPI. Thus, following the completion of Cohort 4, there will be an evaluation period whereby the

Sponsor and the investigators will assess the safety and activity of both Cohorts 3 and 4; if the results are supportive, then enrollment in Cohort 5 will be initiated in patients who have previously failed a CPI.

Patients will receive study treatment in an open-label fashion. Approximately 60 patients were enrolled and received glembatumumab vedotin in Cohort 1. Approximately 30 patients were enrolled in Cohort 2 and received glembatumumab vedotin in combination with varlilumab. Approximately 30 patients will be enrolled in the glembatumumab vedotin and a PD-1 targeted CPI combination Cohort 3. Cohorts 2 and 3 enrolled patients in parallel. Approximately 10-12 patients will be enrolled in Cohort 4 (glembatumumab vedotin in combination with CDX-301) and, if the data is supportive in Cohorts 3 and 4, approximately 30 patients will be enrolled in Cohort 5 (glembatumumab vedotin in combination with both CDX-301 and a PD-1 targeted CPI).

Cohort	Treatment	Glembatumumab Vedotin Dose	Varlilumab 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

Cohort	Treatment	Glembatumumab Vedotin Dose	PD-1 CPI Dose	CDX-301 Dose	Patients (n)
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
4	**Glembatumumab vedotin + CDX-301****	1.9 mg/kg	-	75 µg/kg x 5 days	Approx. 10-12
5	**Glembatumumab vedotin + CDX-301 + PD-1 targeted CPI****	1.9 mg/kg	As per institutional standard of care with reference to the package insert	75 µg/kg x 5 days	Approx. 30

*If >2 treatment-limiting toxicities occur in the first 10 patients, or in >20% of patients thereafter, all further patients enrolled will receive a varlilumab starting dose of 0.3 mg/kg and ongoing patients will also receive any further dosing of varlilumab at 0.3 mg/kg.

**If >2 treatment-limiting toxicities occur in the first 10 patients, or in >20% of patients thereafter, then enrollment in Cohorts 3-5 will be interrupted pending evaluation by Celldex and the investigators.

Study treatment, and associated study visits at 3 week intervals, will continue until disease progression or intolerance. In Cohort 3, patients who previously progressed on nivolumab or pembrolizumab will continue with a PD-1 targeted CPI, nivolumab or pembrolizumab, which will be administered with glembatumumab vedotin until disease progression (using study screening disease assessment as baseline reference) or intolerance. In Cohort 4, two priming cycles of CDX-301 will be administered subcutaneously for 5 consecutive days (Cycle 1 Days -6 to -2 and Cycle 1 Days 15-19) prior to glembatumumab vedotin on Day 1 in Cycles 1 and 2. Glembatumumab vedotin

	will continue to be administered at 3 week intervals until disease progression or intolerance. In Cohort 5, CDX-301 and glembatumumab vedotin will be administered in the same manner as in Cohort 4. Patients in Cohort 5 who previously progressed on nivolumab or pembrolizumab will continue with a PD-1 targeted CPI, nivolumab or pembrolizumab, similar to Cohort 3. Additional hematology and chemistry analyses as well as adverse event monitoring will be performed on Days 7 and 14 in Cycle 1 for patients in Cohorts 2-5. 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 Cohorts 2, 3, and 5 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. In Cohorts 4 and 5, patients should also be observed for at least 1 hour after the first dose of CDX-301, at least 30 minutes for subsequent CDX-301 dosing visits, and for at least 1 hour at all other glembatumumab vedotin 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 (see Section 8.8). 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 2-5, 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 2-5, 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. (See Section 5.6.4 and Section 7.2.4.1.1). Continuous evaluation of toxicity will be performed by the investigators and Celldex throughout the entire course of patient treatment. Treatment-limiting toxicity (as defined in Section 8.7) will be reported to Celldex within 24 hours, and site teleconferences between Celldex and all participating sites will be held at frequent intervals to evaluate emerging safety data. In Cohort 2, if treatment-limiting toxicity occurs in >2 of the first 10 patients, or in >20% of patients thereafter, all further patients enrolled will receive a varlilumab starting dose of 0.3 mg/kg and ongoing patients will also receive any further dosing of varlilumab at 0.3 mg/kg. If additional treatment-limiting toxicity occurs in >20% of patients receiving varlilumab at 0.3 mg/kg, enrollment will be interrupted pending evaluation by Celldex and the investigators. In Cohort 3-5, if treatment-limiting toxicity occurs in >2 of the first 10 patients or in >20% of patients thereafter, then enrollment for the entire cohort will be interrupted pending evaluation by Celldex and the investigators. The FDA and site IRBs will be notified of the analysis and determination regarding further enrollment. Enrollment in Cohort 5 will not commence until the evaluation of toxicity and activity in Cohorts 3 and 4 of all treated patients has been assessed and it has been determined that the combinations of glembatumumab

vedotin with CDX-301 and glembatumumab vedotin with PD-1 targeted CPI are safe and tolerable.

Treatment-Limiting Toxicity (TLT) Definition

Any potential TLT occurring at any time during patient treatment in Cohorts 2-5 will be reported to Celldex within 24 hours of the site's awareness of the occurrence of the event. Any patient who experiences a TLT thought related to varlilumab, the PD-1 targeted CPI, or CDX-301 must discontinue dosing of the suspect drug as dose reductions are not allowed. Glembatumumab vedotin-related toxicity, including TLT, may be managed in accordance with guidance for glembatumumab vedotin dose reductions. Patients who discontinue varlilumab, the PD-1 CPI, or CDX-301 may continue glembatumumab vedotin as monotherapy at the investigator's discretion. Patients in Cohort 2 who discontinue glembatumumab vedotin should discontinue varlilumab. Patients in Cohorts 3 and 5 who discontinue glembatumumab vedotin should discontinue the study treatment phase and may continue PD-1 CPI as per standard of care during study follow up. Patients in Cohorts 4 and 5 who discontinue glembatumumab vedotin should discontinue CDX-301.

In Cohort 2

- All Grade 5 AEs attributed to study treatment **will** be considered TLTs
- ALT of >3 x upper limit of normal (ULN) with a concurrent total bilirubin (TBL) >2 x ULN **will** be considered a TLT if no other reason can be found to explain the combination of increased aminotransferase (AT) and serum TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
- Any Grade 4 AEs attributed to study treatment will be considered TLTs, and any Grade 3 AEs attributed to study treatment will be evaluated by Celldex in collaboration with the investigators as potential TLTs, with the following exceptions (which do not need to be reported within 24 hours as potential TLT):
  - Lymphopenia or any increases in amylase and/or lipase not associated with clinically significant symptoms
  - Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement.
  - Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
  - Grade 3 infusion reaction that resolves within 6 hours to ≤ Grade 1.
  - Grade 3-4 AEs expected as a result of glembatumumab vedotin therapy, (e.g., rash, neuropathy, neutropenia[#]) and not thought to be worsened by the addition of varlilumab will not be considered a TLT; such events should be managed in accordance with guidance for glembatumumab vedotin dose reductions. The overall incidence of study treatment discontinuation due to glembatumumab vedotin-related toxicity will be monitored on an ongoing basis by Celldex and the investigators.

[#]Investigators are referred to the table entitled "Adverse Drug Reactions (ADR) Observed with Glembatumumab Vedotin (Phase II Dose: 1.88 mg/kg, I.V., q3w) in Section 6 of the glembatumumab vedotin investigator's brochure; this table summarizes the adverse drug reactions/expected adverse events considered by

	Celldex to be causally related to glembatumumab vedotin based on clinical experience. For Cohorts 3-5, any treatment-related toxicity that warrants discontinuation of either the PD-1 targeted CPI, CDX-301, or glembatumumab vedotin will be considered a TLT. For all cohorts study analyses will include a retrospective assessment to define the range of gpNMB expression for all enrolled patients and to determine if outcome correlates with intensity or distribution of gpNMB expression. In Cohorts 2 and 3, normal skinfold biopsies are collected prior to study entry for retrospective assessment to identify patients predisposed to rash. Skinfold biopsies will be collected until such time Celldex informs the sites that further data is not needed. 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.
Study Treatment Dosing and Administration	Glembatumumab vedotin will be administered on Day 1 of repeated 21 day cycles in Cohorts 1-5. The starting glembatumumab vedotin dose is 1.9 mg/kg, given as a 90-minute intravenous infusion using a 0.22 micron in-line filter. Treatment will continue until progression or intolerance. In Cohort 2, varlilumab will be administered on Day 1 of Cycles 1, 2, 4, 6, 8, and 10 for a total of up to 6 doses. The dose of varlilumab will be 3.0 mg/kg (or 0.3 mg/kg in the event of treatment-limiting toxicity as described above), administered as a 90-minute intravenous infusion using a volumetric pump with a 0.2 micron pore size, low-protein binding polyethersulfone (PES) membrane in-line filter. In Cohort 2, glembatumumab vedotin and varlilumab will be administered as separate infusions. Varlilumab should be the first infusion and glembatumumab vedotin administered at least 30 minutes after varlilumab infusion. After cycle 10, glembatumumab vedotin treatment as a monotherapy will continue until confirmed progression or intolerance. In Cohort 3, the dose and dosing regimen for the PD-1 targeted CPI will continue per institutional standard of care with reference to the package insert. The first dose of PD-1 targeted CPI may or may not be on the same day of the initiation of glembatumumab vedotin treatment. 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. After initiation of glembatumumab vedotin treatment, CPI will be administered in combination with glembatumumab vedotin until disease progression (using study screening disease assessment as baseline reference) or intolerance. In Cohort 4, two priming cycles of CDX-301 will be administered subcutaneously at a dose of 75 μg/kg for 5 consecutive days (Cycle 1 Days -6 to -2 and Cycle 1 Days 15-19) prior to glembatumumab vedotin on Day 1 in Cycles 1 and 2. Glembatumumab vedotin treatment as a monotherapy will continue to be administered at repeated 21 day cycles until disease progression or intolerance. In Cohort 5, two priming cycles of CDX-301 will be administered subcutaneously at a dose of 75 μg/kg for 5 consecutive days (Cycle 1 Days -6 to -2 and Cycle 1 Days 15-19) prior to glembatumumab vedotin on Day 1 in Cycles 1 and 2. Glembatumumab vedotin

	treatment will continue to be administered at repeated 21 day cycles. The PD-1 targeted CPI will be administered per institutional standard of care with reference to the package insert. 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. After initiation of CDX-301 and glembatumumab vedotin treatment during Cycles 1 and 2, CPI will be administered in combination with glembatumumab vedotin until disease progression (using study screening disease assessment as baseline reference) or intolerance.
Eligibility Criteria	<u>Inclusion Criteria</u> Patients may be included in the study only if they meet all of the following inclusion criteria at the time of study enrollment: 1. Read, understood, and provided written informed consent and, if applicable, Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures 2. Advanced (unresectable Stage III or Stage IV) histologically-confirmed melanoma 3. Documented progressive disease, based on radiographic, clinical or pathologic assessment, during or subsequent to the last anticancer therapy. For Cohorts 3 and 5, progression (confirmed from two scans at least 4 weeks apart) must have occurred during the PD-1 targeted CPI treatment and the investigator has deemed it appropriate to continue to treat beyond confirmed disease progression. 4. No more than 1 prior chemotherapy-containing regimen for advanced disease. For Cohorts 1, 2, and 4, prior treatments received must include at least one check-point inhibitor (e.g., anti-CTLA-4-, PD-1-, PD-L1-targeted immunotherapy) and for patients with a BRAF mutation, at least one BRAF- or MEK-targeted therapy, unless patients are not candidates for, or refused, these therapies. For Cohorts 3 and 5, prior treatment received must include a PD-1 targeted CPI (i.e., nivolumab or pembrolizumab) administered during the most recent disease progression and for patients with a BRAF mutation, at least one BRAF- or MEK-targeted therapy when appropriate. 5. Pre-treatment tumor tissue, and for Cohorts 2 and 3 a skin fold biopsy, available for retrospective evaluation of gpNMB in tumor or normal epithelial cells, respectively, by central immunohistochemistry (IHC): a. All patients in Cohorts 1-3 must submit an archival formalin-fixed and paraffin-embedded (FFPE) tumor tissue sample representative of advanced (Stage III or IV) disease, obtained more than 12 weeks prior to study entry (Historic sample). b. All patients in Cohorts 1-3 are also required to submit a second, recently-obtained FFPE tumor tissue sample (Pre-entry sample). Tissue should be obtained within the 12 weeks prior to study entry, be subsequent to the last systemic anticancer therapy received, and be post-tumor progression. c. All patients in Cohorts 4-5 are required to submit a fresh Pre-entry tumor tissue sample as well as a fresh On-treatment tumor tissue sample. Pre-entry tissue should be obtained within the 12 weeks prior to study entry, be subsequent to the last systemic anticancer therapy received, and be post-tumor progression. Tumor tissue samples will be collected until such time Celldex informs the sites that further data is not needed. For patients who need to undergo a new biopsy to obtain a Pre-entry, or both Pre-entry and On-treatment sample, biopsy sites must be soft tissue or visceral

tumor lesions that can be biopsied with acceptable clinical risk (as judged by the investigator). The biopsy site chosen should have not been previously irradiated. Biopsy sites must be distinct from RECIST 1.1 target lesions, unless, in the case of the Pre-entry biopsy, the biopsy is obtained more than 10 days prior to the Screening Disease Assessment. Patients must be separately consented for collection of a fresh Pre-entry, or both Pre-entry and On-treatment sample.

d. All patients in Cohorts 2 and 3 must agree to submit a recently-obtained FFPE skin fold (axilla or groin) biopsy (Pre-entry sample). Tissue may be obtained by punch biopsy or by surgical excision. Skinfold biopsies will be collected until such time Celldex informs the sites that further data is not needed.

NOTE: Patients who cannot fulfill the requirement for either the Historic, Pre-entry, or On-treatment tumor sample submission in Cohorts 1-5 may be enrolled in the study with prior permission of the Celldex Medical Monitor. In no case will a patient be allowed to enter the study without at least one available tumor sample.

6. Male or female patient ≥ 18 years of age
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (Appendix 4)
8. Life expectancy of ≥ 12 weeks
9. Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (Appendix 3). Target lesions selected for tumor measurements should be those where additional (e.g., palliative) treatments are not indicated or anticipated.
10. Resolution of toxicities related to prior therapies (including radiotherapy) to ≤ NCI-CTCAE Grade 1 severity, except for alopecia, grade 2 fatigue, vitiligo, or endocrinopathies on replacement therapy
11. Screening laboratory values must meet the following criteria:
    - Absolute neutrophil count (ANC) ≥ 1500/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - Platelet count ≥ 100,000/mm^3
    - Calculated creatinine clearance > 40 mL/min per the Cockcroft and Gault formula (Appendix 5) or Serum Creatinine ≤ 2.0 mg/dL
    - Alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN) (≤ 5.0 x ULN in the case of liver metastases)
    - Aspartate transaminase (AST) ≤ 3.0 x ULN (≤ 5.0 x ULN in the case of liver metastases)
    - Total bilirubin ≤ 1.5 x ULN (≤ 5.0 x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.
12. Both men and women enrolled in this trial must use effective contraception during the course of the trial and for at least two months after discontinuing study treatment. Effective contraception is defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge or vaginal ring), intra-uterine device (IUD), implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the patient; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Patients and/or

	partners who are surgically sterile or postmenopausal are exempt from this requirement. Exclusion Criteria Patients will be excluded from the study for any of the following reasons: 1. Received glembatumumab vedotin (CR011-vcMMAE; CDX-011) or other MMAE-containing agents previously 2. BRAF/MEK inhibitors within 2 weeks prior to the first dose of study treatment 3. Use of any monoclonal based therapies within 4 weeks, except for the PD-1 targeted CPI (i.e., nivolumab or pembrolizumab) in Cohort 3, and all other immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) within 2 weeks, prior to the first dose of study treatment 4. Chemotherapy within 21 days or at least 5 half-lives (whichever is longer) prior to the planned start of study treatment 5. [criterion deleted] 6. Major surgery within 4 weeks prior to the first dose of study treatment. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and patients should be recovered. 7. Use of other investigational drugs within 2 weeks or 5 half-lives (whichever is longer) prior to study treatment administration 8. Patients with ocular melanoma 9. Neuropathy > NCI-CTCAE Grade 1 10. Subjects with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin. Compounds of similar composition include Auristatin PHE as an anti-fungal agent, Auristatin PE (TZT-1027, Soblidotin, NSC-654663) as an anti-tumor agent and symplostatin 1 as an anti-tumor agent. 11. Active, untreated central nervous system metastases, except for patients with ≤ 3 small (< 0.6 cm) asymptomatic lesions where treatment is not indicated. Patients with brain metastases identified at Screening may be rescreened after the lesion(s) have been appropriately treated; patients with treated brain metastases should be neurologically stable for 4 weeks post-treatment and prior to study enrollment, and off corticosteroids for at least 2 weeks before administration of study drugs. 12. Women who are pregnant or lactating. All female patients with reproductive potential must have a negative pregnancy test prior to starting treatment. 13. History of alternate malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated *in situ* disease, or any other cancer from which the patient has been disease-free for ≥ 3 years 14. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension or arrhythmia, congestive heart failure (New York Heart Association Class III or IV) related to primary cardiac disease, ischemic or severe valvular heart disease or a myocardial infarction within 6 months prior to the first dose of study treatment 15. Known alcohol or drug abuse 16. Known infection with Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) or Hepatitis C (HCV) 17. Any underlying medical condition that, in the investigator's opinion, will make the administration of glembatumumab vedotin hazardous to the patient, or would obscure the interpretation of toxicity determination or adverse events

	Additional Exclusion Criteria for Cohort 2 Only In addition to the exclusion criteria above, patients will be excluded from Cohort 2 for the following reason: 18. Previous treatment with varlilumab or any other anti-CD27 mAb Additional Exclusion Criteria for Cohorts 2-5 In addition to the exclusion criteria above, patients will be excluded from Cohorts 2-5 for the following reasons: 19. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment 20. Use of immunosuppressive medications within 4 weeks or systemic corticosteroids within 2 weeks prior to first dose of study treatment. Topical, inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Non-absorbed intraarticular corticosteroid and replacement steroids (≤10 mg/day prednisone or equivalent) will be permitted. 21. Active autoimmune disease or a documented history of autoimmune disease, or history of potential autoimmune syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo, endocrinopathies, type 1 diabetes, or patients with resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger (e.g., drug-related serum sickness or post-streptococcal glomerulonephritis). Subjects with mild asthma who require intermittent use of bronchodilators (such as albuterol) who have not been hospitalized for asthma in the preceding 3 years will not be excluded from this study. Additional Exclusion Criteria for Cohorts 3 and 5 Only In addition to the exclusion criteria above, patients will be excluded from Cohorts 3 and 5 for the following reasons: 22. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. 23. Active diverticulitis. Additional Exclusion Criteria for Cohorts 4 and 5 Only In addition to the exclusion criteria above, patients will be excluded from Cohorts 4 and 5 for the following reasons: 24. Any non-study vaccination within 4 weeks, or influenza vaccine within 2 weeks, prior to CDX-301 dosing
Criteria for Evaluation	Anti-tumor activity evaluations Anti-tumor activity will be assessed via ORR, PFS, DOR, and OS. Tumor response and progression will be defined by the investigator, according to RECIST 1.1 criteria. For Cohorts 2-5, supplementary retrospective analyses of tumor response and progression may also be performed using irRECIST criteria. Safety Safety will be assessed by vital sign measurements, clinical laboratory tests, physical exams, ECGs, ECOG performance status, and the incidence and severity of adverse events (graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE v 4.0.)). Given the expected mechanism of action of varlilumab, the PD-1 targeted CPI, and CDX-301, particular attention will be given to

	adverse events in Cohorts 2-5 that may be secondary to activation of the immune system and have been observed with other immune-stimulatory antibodies (see Section 8.8). Immunogenicity Patients will be monitored for the development of anti-glembatumumab vedotin and anti-CR011 antibodies. In addition, patients in Cohort 2 will be monitored for anti-varlilumab antibodies and patients in Cohorts 4 and 5 will be monitored for anti-CDX-301 antibodies. Additional analyses will assess whether these antibodies are neutralizing. Pharmacokinetics (PK) Concentration of the glembatumumab vedotin antibody-drug conjugate (ADC), total antibody (TA), and free MMAE (Cohorts 1-5), varlilumab (Cohort 2), and CDX-301 (Cohorts 4 and 5) will be determined using Good Laboratory Practices (GLP) compliant enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The impact of circulating gpNMB levels or other soluble mediators on glembatumumab vedotin pharmacokinetic parameters may also be examined. Pharmacodynamic (PD) parameters Pharmacodynamic parameters will be evaluated via assessment of post-treatment tumor tissue obtained via voluntary biopsy or resection (Cohorts 1-3), mandatory pre-study and on-treatment biopsies (Cohorts 4 and 5), and blood samples. Parameters evaluated may include localization of glembatumumab vedotin, CR011, or MMAE at the tumor site and/or gpNMB expression levels in serum and tumor tissue, as well as evaluation of other soluble mediators, tumor infiltrating and peripheral leukocytes, circulating tumor cells, other immune response cells of interest such as gpNMB-expressing myeloid-derived suppressor cells, and to investigate the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations (Cohorts 4 and 5). Additional analysis may include immune response assessment to potentially relevant tumor antigens.
Statistical Methods	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 for reasons unrelated to study treatment will be excluded from the response-evaluable population, 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, 3, and 5, ORR by RECIST 1.1 remains the primary endpoint. Supplementary analyses of tumor response and progression may also be performed for Cohorts 2-5 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, 3, and 5, approximately 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. Cohort 4 will enroll approximately 10-12 patients for safety and tolerability assessment of glembatumumab vedotin and CDX-301. Pre- and on-study tumor biopsies will be analyzed for the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations. The anti-tumor activity will also be explored as a secondary endpoint. Patients in Cohorts 2-5 who experience an event determined to be a treatment-limiting toxicity will not be replaced and will be considered evaluable. All statistical analyses will be performed separately for each treatment cohort, unless specified differently. Given the timing of different cohorts, statistical analyses will be performed for each cohort when sufficient data is available upon completion of enrollment. ORR will be estimated as the proportion of patients who achieve best overall response of CR or PR per RECIST 1.1 that are confirmed at an interval of at least 28 days. Secondary analyses of ORR will include responses observed at a single-time point. The final analysis of ORR will be based on the investigator assessment of response. However, in the event of a positive study outcome, an additional assessment of ORR may be performed by an independent review committee (IRC). The estimate of the objective response rate will be accompanied by one- and two-sided exact 95% Clopper-Pearson confidence interval for each cohort. In addition, one-sample exact binomial test will be used to test the null hypotheses of ORR (Cohort 1: ORR $\leq$5%; Cohorts 2, 3, and 5: both ORR $\leq$5%, and ORR $\leq$10%) with one-sided significance level of 0.05 for Cohort 1 and 0.1 for Cohorts 2, 3, and 5. The primary ORR analyses will be based on respective evaluable population and the secondary analysis will be based on respective ITT population. Supplementary analyses of tumor response and progression may also be performed using irRECIST criteria (in which new lesions do not constitute progression, but contribute to the calculated sum of diameter of all measurable disease). Exploratory analysis will be performed for comparing the three cohorts on efficacy endpoints, and no adjustment for multiple testing will be considered. Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest diameters of target lesions. Correlation between the degree of gpNMB expression and maximum decrease from baseline in the sum of longest diameters of target lesions will be evaluated. For this analysis, all patients will be used, with gpNMB expression measured on a continuous scale (percentage of gpNMB-positive tumor cells). Further, to explore the predictive power of various cut-off values for gpNMB expression, a receiver operating curve (ROC) analysis for the response data (Gönen and SAS Institute. 2007) will be performed. The duration of objective response, PFS, and OS will be summarized descriptively for all patients, using the Kaplan-Meier method. The association between the degree of gpNMB expression and PFS will be evaluated using a Cox proportional hazards model. For this analysis, all patients will be used, with gpNMB expression measured on a continuous scale (percentage of gpNMB-positive tumor cells). When a factor is continuous, the hazard ratio is interpreted as the change in risk for each 1-unit increase in the factor. For example, a hazard ratio of 0.99 indicates the hazard for the event decreases by 1% for each 1%-unit increase in gpNMB expression level. For Cohort 1, if a true hazard ratio of 0.99 is assumed and the standard deviation for gpNMB expression level is ± 35%, 36 PFS events from among the 52 evaluable patients (70% event rate)

	will provide approximately 80% power with one-sided significance level of 10% (Hsieh and Lavori 2000). The predictive power of various cut-off values for gpNMB expression will be explored based on a receiver operating curve (ROC) analysis for censored data (Gönen and SAS Institute. 2007). Similar analyses will be performed for Cohorts 2, 3, and 5 separately. 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.

4. SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments (Cohorts 1-3)

Visit	Screening[2]	Treatment Visits[3]						Disease Assessment Visit[5]	Survival Assessment[6]
		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]	*Every 6 (±1) weeks for 6 months then every 9 (±2) weeks thereafter*	*Every 12 (±2) weeks until study closure*
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							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									X
Concomitant medication review[24]	X	X	X	X	X	X	X	X	X
Adverse event monitoring[25]		X	X[26]	X[26]	X	X	X	X[27]	X[27]

(footnotes on next page)

Table 1 - Footnotes:

1. 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 (Section 8.6) and (Section 8.8) for management of dosing delays due to toxicity.
2. 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.
3. Patients will receive study treatment until intolerance, progression of disease, or any of the other criteria for discontinuation of study treatment (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.
4. The End of Treatment Visit should be performed within 28 days after last dose of study treatment and prior to initiation of alternate therapies.
5. 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) (Section 5.6.4 and 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.
6. 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.
7. 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.
8. 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 (Cohorts 2 and 3) must be obtained within 12 weeks of study entry.
9. 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.

10. 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.
11. Complete physical exam should be performed at screening; thereafter, symptom-directed exams are acceptable.
12. Assessments do not need to be repeated if completed within the previous 24 hours as part of the screening assessment.
13. 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.)
14. 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.
15. 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.

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

16. Samples for immunogenicity will be collected prior to dosing on Day 1 of "odd" cycles (i.e., Cycles 1, 3, 5, 7, etc.).
17. Analyses will be performed centrally. Sample collection, processing and shipping instructions will be provided separately.

18. 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 Cohorts 2 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.
19. 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.
    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.
    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.
    For Cohorts 1, 2, and 3, analysis may also include circulating soluble gpNMB levels or other soluble molecules.
20. 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.
21. 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.
22. 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.

23. 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 3 doses of nivolumab or 2 doses of pembrolizumab 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.
    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.
24. 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.
25. 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.
26. 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.
27. 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.

Table 2. Schedule of Assessments (Cohorts 4 and 5)

Visit	Screening[2]	Treatment Visits[3]							Disease Assessment Visit[5]	Survival Assessment[6]
		Cycle 1/ Day -6 to Day -2	Cycle 1 / Day 1	Cycle 1 / Day 7	Cycle 1 / Day 15-19	Cycle 2 / Day 1	Cycle 3, 4, 5, etc. / Day 1	End of Treatment[4]	*Every 6 (±1) weeks for 6 months then every 9 (±2) weeks thereafter*	*Every 12 (±2) weeks until study closure*
Visit window[1]	*Day -35 to Day -7*		*+3/- 1 days*	*+/- 1 day*		*+3/- 1 days*	*+/- 3 days*	*Within 28 days post-dosing*		
Informed Consent, and, if applicable, HIPAA	X									
Tumor tissue[7]	X[8]			X[8]	X[9]					
Medical history[10]	X	X (Day -6 only)								
Physical examination[11]	X	X[12]	X		X	X	X	X		
Vital signs[13]	X	X	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] (Day -6 only)	X	X	X (Day 15 only)	X	X	X		
Blood chemistry[15]	X	X[12] (Day -6 only)	X	X	X (Day 15 only)	X	X	X		
Urinalysis/dipstick[15]	X	X[12]						X		
Immunogenicity[16, 17]		X					X (Odd cycles)	X		
PBMC collection[17, 18]		X (Day -6 only)			X (Day 15 only)	X	X (Cycle 3 only)			
PK sample collection[17, 19]		X (Days -6 and -2 only)	X		X (Days 15 and 19 only)	X	X (odd cycles)	X		
PD sample collection[17]		X	X			X		X		
Disease Assessment[20]	X								X	
Administration of glembatumumab vedotin[21]			X			X	X			
Administration of CDX-301[21, 22]		X			X					
Administration of PD-1 targeted CPI (Cohort 5)[23]			X	X						
Survival status										X
Concomitant medication review[24]	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring[25]		X	X	X[26]	X	X	X	X	X[27]	X[27]

(footnotes on next page)

Table 2 - Footnotes:

1. 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 (Section 8.6) and (Section 8.8) for management of dosing delays due to toxicity.
2. 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.
3. Patients will receive study treatment until intolerance, progression of disease, or any of the other criteria for discontinuation of study treatment (Section 7.2.4.1.1) are met. Both cohorts will receive glembatumumab vedotin on a three-week cycle. Patients will also receive CDX-301 on 5 consecutive days from Cycle 1 Days -2 to -6 and Cycle 1 Days 15-19. Cohort 5 patients will also receive a PD-1 targeted CPI per institutional standard of care.
4. The End of Treatment Visit should be performed within 28 days after last dose of study treatment and prior to initiation of alternate therapies.
5. 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. 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) (Section 5.6.4 and 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.
6. 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.
7. Assessment of gpNMB expression and/or dendritic cells will be performed by IHC, retrospectively, at a central laboratory on FFPE Pre-entry and On-treatment tumor samples. 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. For these analyses, fresh Pre-entry and On-treatment samples will need to be cut into two pieces. Sample collection, processing and shipping instructions will be provided separately. Tumor tissue samples will be collected until such time Celldex informs the sites that further data is not needed.
8. Fresh pre-entry 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. On-treatment biopsies must be obtained on Cycle 1 Day 7 (+/- 1 day). On-treatment biopsies in Cohort 5 may be collected at a different time point depending on the results obtained in Cohort 4. If so, then any change will be communicated to the Investigators and sites. Sites of sample collection must be soft tissue tumor or visceral lesions that can be attained with acceptable clinical risk (as judged by the investigator). The site chosen should not have been previously irradiated and must be distinct from RECIST 1.1 target lesions.
9. 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.
10. Medical history includes demography, melanoma history, previous surgeries/therapy, and pre-existing diseases. At Cycle 1, Day -6, medical history is updated prior to administration of study drug.

11. Complete physical exam should be performed at screening; thereafter, symptom-directed exams are acceptable.
12. Assessments do not need to be repeated if completed within the previous 24 hours as part of the screening assessment.
13. Vital signs to include height (at screening only), weight, respiration, pulse, temperature, and resting systolic and diastolic blood pressure. 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. On CDX-301 dosing days, vital signs should be performed prior to dosing and 60 (±10) minutes after the first dose of CDX-301, and prior to dosing and 30 (±10) minutes after subsequent doses of CDX-301. 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.)
14. 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.
15. 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
Erythrocyte count (RBC)	Bicarbonate	Specific gravity
Leukocytes (WBC)	Glucose (nonfasting)	Blood
Platelets	Blood urea nitrogen (BUN)	
Differential:	Creatinine	*Microscopic examination must be performed at*
Neutrophils	Calcium	*baseline and, if clinically indicated, at subsequent*
Lymphocytes	Phosphate	*visits (if urinary infection is suspected then a negative*
Monocytes	Alkaline phosphatase	*urine culture is required prior to enrollment.)*
Eosinophils	Alanine transaminase (ALT/SGPT)	
	Aspartate transaminase (AST/SGOT)	
Differential should be reported consistently	Total protein	
throughout the study as either an absolute	Albumin	
count (preferred) or as a percentage.	Lactate Dehydrogenase (LDH)	
	Total Bilirubin	

16. Samples for CDX-301 and glembatumumab vedotin immunogenicity will be collected prior to dosing on Day -6 of Cycle 1 and Day 1 of "odd" cycles (i.e., Cycles 1, 3, 5, 7, etc.), and at the End of Treatment Visit.
17. Analyses will be performed centrally. Sample collection, processing and shipping instructions will be provided separately.
18. For Peripheral Blood Mononuclear Cell (PBMC) collection on Cycle 1/Day -6, Cycle 1/Day 15, Cycle 2/Day 1, and Cycle 3/Day 1, samples are collected 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.
19. On Cycle 1 Days -2, -6, 15, and 19, sample for CDX-301 PK is collected prior to CDX-301 dose. On Day 1 of Cycle 1 and 2 only, glembatumumab vedotin PK samples will be collected prior to any dosing and at the end of infusion (at or within 30 minutes after completion of infusion). A PK sample for both analytes will also be collected prior to dosing on Day 1 of "odd" cycles (i.e., Cycles 3, 5, 7, etc.) and at the End of Treatment visits.

20. 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.
21. 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.
22. The intent is for CDX-301 to be administered for 5 consecutive days on Monday through Friday, followed by glembatumumab vedotin treatment (and PD-1 targeted CPI for Cohort 5) on the following Monday. CDX-301 administration is allowed on weekend days if the site has the ability to do so. Ideally, CDX-301 should be administered at approximately the same time each day. Patients should be observed on Day -6 prior to Cycle 1 for at least 1 hour after CDX-301 injection, and for at least 30 minutes at all subsequent CDX-301 doses.
23. In Cohort 5, 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 3 doses of nivolumab or 2 doses of pembrolizumab 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, in Cohort 5, 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 should be observed on Cycle 1 Day 1 for at least 2 hours after administration of 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.
    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.
24. 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.
25. 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
26. Adverse event monitoring on Cycle 1 Day 7 can be performed in person or by telephone to determine if the patient is experiencing any adverse events.
27. Events occurring >28 days after discontinuation of glembatumumab vedotin, >28 days after discontinuation of CDX-301, or >70 days after discontinuation of the PD-1 targeted CPI (Cohort 5 only) are only reportable if both serious (SAE) and potentially treatment-related.

[redacted]

6. STUDY OBJECTIVES

The primary objective of the study is to evaluate the anti-cancer activity of glembatumumab vedotin as monotherapy (Cohort 1), in combination with varlilumab (Cohort 2), in combination with a PD-1 targeted checkpoint inhibitor (CPI) (Cohort 3), or in combination with glembatumumab vedotin, CDX-301, and a PD-1 targeted CPI (Cohort 5) in advanced melanoma as measured by the ORR per RECIST 1.1. In Cohort 4, the primary objective is to evaluate the safety and tolerability of the combination of glembatumumab vedotin and CDX-301.

Secondary objectives are:

- To further assess the anti-cancer activity of glembatumumab vedotin as monotherapy, in combination with varlilumab, in combination with a PD-1 targeted CPI, or in combination with CDX-301 and a PD-1 targeted CPI in advanced melanoma, as assessed by PFS, DOR and OS. To assess the anti-cancer activity of the combination of glembatumumab vedotin and CDX-301 in advanced melanoma, as assessed by ORR, PFS, DOR, and OS.

- To investigate if the anti-cancer activity of glembatumumab vedotin alone or in combination with immunotherapies 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 immunotherapies in advanced melanoma

Exploratory objectives are:

- 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; analysis of peripheral blood subsets; to investigate the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations (Cohorts 4 and 5).
- To further characterize the pharmacokinetics and immunogenicity of glembatumumab vedotin, varlilumab, and CDX-301 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 immunotherapies as measured by the ORR and PFS per irRECIST

7. INVESTIGATIONAL PLAN

7.1. Overall Design and Plan of the Study

This is an open-label Phase II study of glembatumumab vedotin as monotherapy or in combination with varlilumab, or in combination with other immunotherapies, in patients with unresectable Stage III or IV melanoma who have previously received checkpoint inhibitors. Patients will receive study treatment in an open-label fashion. Approximately 60 patients were enrolled and received glembatumumab vedotin monotherapy in Cohort 1. Approximately 30 patients were enrolled in Cohort 2 and received glembatumumab vedotin in combination with varlilumab. In Cohort 3, approximately 30 patients will receive glembatumumab vedotin in combination with a PD-1 targeted checkpoint inhibitor (CPI); nivolumab and pembrolizumab. In this cohort, patients whose last treatment regimen included nivolumab or pembrolizumab, and per institutional standard of care would continue to receive a PD-1 targeted therapy despite progression, will receive either nivolumab or pembrolizumab in combination with glembatumumab vedotin, to determine whether the addition of glembatumumab vedotin can induce an effective anti-melanoma immune response and improved anti-cancer activity. Patients who previously received nivolumab in combination with ipilimumab and have discontinued ipilimumab would continue with nivolumab, or pembrolizumab, in combination with glembatumumab vedotin. Patients who experienced disease progression on nivolumab may receive nivolumab or pembrolizumab in combination with glembatumumab vedotin.

Patients who experienced disease progression on pembrolizumab may receive nivolumab or pembrolizumab in combination with glembatumumab vedotin.

In Cohort 4, approximately 10-12 patients will receive glembatumumab vedotin combined with CDX-301 to determine the safety and tolerability of the combination and to investigate the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations. Following this pilot cohort, an evaluation period will occur whereby the Sponsor and Investigators will assess the safety and activity of glembatumumab vedotin in combination with CDX-301 (Cohort 4) and with a PD-1 targeted CPI (Cohort 3). If the results are supportive in Cohorts 3 and 4, then enrollment of approximately 30 patients in Cohort 5 will begin to evaluate whether the anti-tumor immune responses would likely be further augmented by combining all three agents in patients who have previously failed a CPI.

Study treatment, and associated study visits at 3 week intervals, will continue until disease progression or intolerance. In Cohort 2, varlilumab will be administered on Day 1 of Cycles 1, 2, 4, 6, 8, and 10 for a total of up to 6 doses. In Cohort 3, patients who experienced disease progression on nivolumab or pembrolizumab will continue with a PD-1 targeted CPI, nivolumab or pembrolizumab, which will be administered with glembatumumab vedotin until disease progression (using study screening disease assessment as baseline reference) or intolerance. In Cohort 4, two priming cycles of CDX-301 will be administered subcutaneously for 5 consecutive days (Cycle 1 Days -6 to -2 and Cycle 1 Days 15-19) prior to glembatumumab vedotin on Day 1 in Cycles 1 and 2. Glembatumumab vedotin will continue to be administered at 3 week intervals until disease progression or intolerance. Patients in Cohort 5 who previously progressed on nivolumab or pembrolizumab will continue with a PD-1 targeted CPI, nivolumab or pembrolizumab, similar to Cohort 3. The PD-1 targeted CPI will be administered according to institutional standard of care with reference to the package insert. In Cohort 5, CDX-301 and glembatumumab vedotin will be administered in the same manner as in Cohort 4.

Additional hematology and chemistry analyses as well as adverse event monitoring will be performed on Days 7 and 14 in Cycle 1 for patients in Cohorts 2-5. 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 Cohorts 2 and 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. Patients in Cohorts 4 and 5 should be observed on Cycle 1 Day -6 and Cycle 1 Day 1 for at least 2 hours after the last study drug, and for at least 1 hour at all other 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 (see Section 8.8). 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 2-5, 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 2-5, 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) (Section 7.2.4.1.1). The following criteria must be met: 1) the patient experiences investigator-assessed clinical benefit; and 2) the patient is tolerating the study treatment. The patient must sign an informed consent form for continued treatment after apparent disease progression.

Continuous evaluation of toxicity will be performed by the investigators and Celldex throughout the entire course of patient treatment. Treatment-limiting toxicity (as defined in Section 8.7) will be reported to Celldex within 24 hours, and site teleconferences between Celldex and all participating sites will be held at frequent intervals to evaluate emerging safety data. In Cohort 2, if treatment-limiting toxicity occurs in >2 of the first 10 patients, or in >20% of patients thereafter, all further patients enrolled will receive a varlilumab starting dose of 0.3 mg/kg and ongoing patients will also receive any further dosing of varlilumab at 0.3 mg/kg. If additional treatment-limiting toxicity occurs in >20% of patients receiving varlilumab at 0.3 mg/kg, enrollment will be interrupted pending evaluation by Celldex and the investigators. In Cohorts 3-5, if >2 of the first 10 patients experience treatment-limiting toxicities, or in >20% of patients thereafter, then enrollment in the cohort will be interrupted pending evaluation by Celldex and the investigators. The FDA and site IRBs will be notified of the analysis and determination regarding further enrollment. Enrollment in Cohort 5 will not commence until the evaluation of toxicity and activity in Cohorts 3 and 4 of all treated patients has been assessed and it has been determined that the combinations of glembatumumab vedotin with CDX-301 and glembatumumab vedotin with PD-1 targeted CPI are safe and tolerable.

For all cohorts, study analyses will include a retrospective assessment to define the range of gpNMB expression for all enrolled patients and to determine if outcome correlates with intensity or distribution of gpNMB expression. In Cohorts 2 and 3, normal skinfold biopsies are collected prior to study entry for retrospective assessment to identify patients predisposed to rash. Skinfold biopsies will be collected until such time Celldex informs the sites that further data is not needed.

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.

7.2. Selection of Study Population

7.2.1. Number of Patients

Approximately 160 patients will be enrolled: approximately 60 patients enrolled in Cohort 1, approximately 30 patients enrolled in Cohort 2, approximately 30 patients will be enrolled in Cohort 3, approximately 10-12 patients will be enrolled in Cohort 4, and approximately 30 patients will be enrolled in Cohort 5. Cohorts 2 and 3 enrolled patients in parallel.

7.2.2. Subject Eligibility

7.2.2.1. Inclusion Criteria

Patients may be included in the study only if they meet all of the following inclusion criteria at the time of study enrollment:

1. Read, understood, and provided written informed consent and, if applicable, Health Insurance Portability and Accountability Act (HIPAA) authorization after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.
2. Advanced (unresectable Stage III or Stage IV) histologically-confirmed melanoma.
3. Documented progressive disease, based on radiographic, clinical or pathologic assessment, during or subsequent to the last anticancer therapy. For Cohorts 3 and 5, progression (confirmed from two scans at least 4 weeks apart) must have occurred during the PD-1 targeted CPI treatment and the investigator has deemed it appropriate to continue to treat beyond confirmed disease progression.
4. No more than 1 prior chemotherapy-containing regimen for advanced disease. For Cohorts 1, 2, and 4, prior treatments received must include at least one check-point inhibitor (e.g., anti-CTLA-4-, PD-1-, PD-L1-targeted immunotherapy) and for patients with a BRAF mutation, at least one BRAF- or MEK-targeted therapy, unless patients are not candidates for, or refused, these therapies. For Cohorts 3 and 5, prior treatment received must include a PD-1 targeted CPI (i.e., nivolumab or pembrolizumab) administered during the most recent disease progression and for patients with a BRAF mutation, at least one BRAF- or MEK-targeted therapy when appropriate.
5. Pre-treatment tumor tissue, and for Cohorts 2 and 3 a skin biopsy, available for retrospective evaluation of gpNMB in tumor or normal epithelial cells, respectively, by central immunohistochemistry (IHC):
    a. All patients in Cohorts 1-3 must submit an archival FFPE tumor tissue sample representative of advanced (Stage III or IV) disease, obtained more than 12 weeks prior to study entry (Historic sample).
    b. All patients in Cohorts 1-3 are also required to submit a second, recently-obtained FFPE tumor tissue sample (Pre-entry sample). Tissue should be obtained within the 12 weeks prior to study entry, be subsequent to the last systemic anticancer therapy received, and be post-tumor progression.
    c. All patients in Cohorts 4-5 are required to submit a fresh Pre-entry tumor tissue sample

as well as a fresh On-treatment tumor tissue sample. Pre-entry tissue should be obtained within the 12 weeks prior to study entry, be subsequent to the last systemic anticancer therapy received, and be post-tumor progression. Tumor tissue samples will be collected until such time Celldex informs the sites that further data is not needed.

For patients who need to undergo a new biopsy to obtain a Pre-entry, or both Pre-entry and On-treatment, sample, biopsy sites must be soft tissue or visceral tumor lesions that can be biopsied with acceptable clinical risk (as judged by the investigator). The biopsy site chosen should have not been previously irradiated. Biopsy sites must be distinct from RECIST 1.1 target lesions, unless, in the case of the Pre-entry biopsy, the biopsy is obtained more than 10 days prior to the Screening Disease Assessment. Patients must be separately consented for collection of a fresh Pre-entry, or both Pre-entry and On-treatment sample.

d. All patients in Cohorts 2 and 3 must agree to submit a recently-obtained FFPE skin fold (axilla or groin) biopsy (Pre-entry sample). Tissue may be obtained by punch biopsy or surgical excision. Skinfold biopsies will be collected until such time Celldex informs the sites that further data is not needed.

NOTE: Patients who cannot fulfill the requirement for either the Historic, Pre-entry, or On-treatment sample submission in Cohorts 1-5 may be enrolled in the study with prior permission of the Celldex Medical Monitor. In no case will a patient be allowed to enter the study without at least one available tumor sample.

6. Male or female patient ≥ 18 years of age
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (Appendix 4)
8. Life expectancy of ≥ 12 weeks
9. Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (Appendix 3). Target lesions selected for tumor measurements should be those where additional (e.g., palliative) treatments are not indicated or anticipated.
10. Resolution of toxicities related to prior therapies (including radiotherapy) to ≤ NCI-CTCAE Grade 1 severity, except for alopecia, grade 2 fatigue, vitiligo, or endocrinopathies on replacement therapy
11. Screening laboratory values must meet the following criteria:

- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Hemoglobin ≥ 9.0 g/dL
- Platelet count ≥ 100,000/mm^3
- Calculated creatinine clearance > 40 mL/min per the Cockcroft and Gault formula (Appendix 5) or Serum Creatinine ≤ 2.0 mg/dL
- Alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN) (≤ 5.0 x ULN in the case of liver metastases)
- Aspartate transaminase (AST) ≤ 3.0 x ULN (≤ 5.0 x ULN in the case of liver metastases)

- Total bilirubin ≤ 1.5 x ULN (≤ 5.0 x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL

12. Both men and women enrolled in this trial must use effective contraception during the course of the trial and for at least two months after discontinuing study treatment. Effective contraception is defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge or vaginal ring), intra-uterine device (IUD), implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the patient; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.

7.2.2.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. Received glembatumumab vedotin (CR011-vcMMAE; CDX-011) or other MMAE-containing agents previously
2. BRAF/MEK inhibitors within 2 weeks prior to the first dose of study treatment.
3. Use of any monoclonal based therapies within 4 weeks, except for the PD-1 targeted CPI (i.e., nivolumab or pembrolizumab) in Cohort 3, and all other immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) within 2 weeks, prior to the first dose of study treatment.
4. Chemotherapy within 21 days or at least 5 half-lives (whichever is longer) prior to the planned start of study treatment
5. [criterion deleted]
6. Major surgery within 4 weeks prior to the first dose of study treatment. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and patients should be recovered.
7. Use of other investigational drugs within 2 weeks or 5 half-lives (whichever is longer) prior to study treatment administration
8. Patients with ocular melanoma
9. Neuropathy > NCI-CTCAE Grade 1
10. Subjects with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin. Compounds of similar composition include Auristatin PHE as an anti-fungal agent, Auristatin PE (TZT-1027, Soblidotin, NSC-654663) as an anti-tumor agent and symplostatin 1 as an anti-tumor agent.
11. Active, untreated central nervous system metastases, except for patients with ≤ 3 small (< 0.6 cm) asymptomatic lesions where treatment is not indicated. Patients with brain metastases identified at Screening may be rescreened after the lesion(s) have been appropriately treated; patients with treated brain metastases should be neurologically stable for 4 weeks post-treatment and prior to study enrollment, and off corticosteroids for at least 2 weeks before administration of study drugs.

12. Women who are pregnant or lactating. All female patients with reproductive potential must have a negative pregnancy test prior to starting treatment.
13. History of alternate malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated *in situ* disease, or any other cancer from which the patient has been disease-free for ≥ 3 years
14. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension or arrhythmia, congestive heart failure (New York Heart Association Class III or IV) related to primary cardiac disease, ischemic or severe valvular heart disease or a myocardial infarction within 6 months prior to the first dose of study treatment
15. Known alcohol or drug abuse
16. Known infection with Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) or Hepatitis C (HCV)
17. Any underlying medical condition that, in the investigator's opinion, will make the administration of glembatumumab vedotin hazardous to the patient, or would obscure the interpretation of toxicity determination or adverse events

Additional Exclusion Criteria for Cohort 2 Only

In addition to the exclusion criteria above, patients will be excluded from Cohort 2 for the following reason:

18. Previous treatment with varlilumab or any other anti-CD27 mAb

Additional Exclusion Criteria for Cohorts 2-5

In addition to the exclusion criteria above, patients will be excluded from Cohorts 2-5 for the following reasons:

19. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment.
20. Use of immunosuppressive medications within 4 weeks or systemic corticosteroids within 2 weeks prior to first dose of study treatment. Topical, inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Non-absorbed intraarticular corticosteroid and replacement steroids (≤10 mg/day prednisone or equivalent) will be permitted.
21. Active autoimmune disease or a documented history of autoimmune disease, or history of potential autoimmune syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo, endocrinopathies, type 1 diabetes, or patients with resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger (e.g., drug-related serum sickness or post-streptococcal glomerulonephritis). Subjects with mild asthma who require intermittent use of bronchodilators (such as albuterol) who have not been hospitalized for asthma in the preceding 3 years will not be excluded from this study.

Additional Exclusion Criteria for Cohorts 3 and 5 Only

In addition to the exclusion criteria above, patients will be excluded from Cohorts 3 and 5 for the following reasons:

22. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
23. Active diverticulitis

Additional Exclusion Criteria for Cohorts 4 and 5 Only

In addition to the exclusion criteria above, patients will be excluded from Cohorts 4 and 5 for the following reasons:

24. Any non-study vaccination within 4 weeks, or influenza vaccine within 2 weeks, prior to CDX-301 dosing

7.2.3. Measures to Minimize Bias

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

7.2.4. Withdrawals and Replacement of Patients

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

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.

7.2.4.1. Discontinuation of Study Treatment

Reasons for discontinuation of study treatment include:

- Progressive disease, as assessed by the treating investigator in accordance with RECIST 1.1 criteria (Appendix 3); in Cohorts 2-5 an exception may be granted as described in Section 7.2.4.1.1.
- Symptomatic deterioration (clinical progression):
  - Note: This category is applicable to patients with a global deterioration of health status requiring discontinuation of treatment. However, per RECIST 1.1 (Appendix 3), symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. Thus, every effort should be made to continue disease

assessments per protocol until documented objective progression or initiation of alternate therapy.

- Receipt of alternate anti-cancer treatments
- Withdrawal request by the patient or the patient's legal representative
  - Note: Withdrawal of consent for continued treatment should be differentiated from withdrawal of consent for study follow-up, and every effort should be made within the bounds of safety and patient choice to have each patient complete the study follow-up.
- Adverse Event
- Physician Decision
- Non-compliance of the patient
- Pregnancy
- Death, otherwise not explainable by the above options
- Patient lost to follow-up (see below)
- Treatment-limiting toxicity (Cohorts 2-5)

Patients who discontinue study treatment should be seen for an End of Treatment Visit. Patients who discontinue study treatment without progression of disease as per RECIST 1.1 should continue Disease Assessment Visits until criteria for disease progression are met or alternate therapies are initiated (see Table 1, and Table 2).

7.2.4.1.1 Allowance for Permitting Continued Study Drug Treatment in Cases of Apparent Progressive Disease

As described in Section 5.6.4, accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progression per RECIST (Appendix 3). Therefore, in order to ascertain whether true progression has occurred, or whether a treatment mediated inflammatory/immune mediated antitumor reaction (pseudoprogression) might have preceded a tumor response, patients with apparent progression who have no additional conventional treatment options may continue study treatment and complete the subsequent disease assessment on schedule, provided the following criteria are met:

- Investigator-assessed clinical benefit. The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment.
- Patient is tolerating study drug.
- All decisions to continue treatment beyond initial progression must be discussed with the Celldex Medical Monitor and the patient, and the patient must sign an informed consent form for continued treatment after initial progression. Patients can only continue study treatment beyond initial progression if they have no additional conventional treatment options.

- Patients should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions). For this assessment, new lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesions considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).
- For statistical analyses that include the investigator-assessed progression date, patients who continue treatment beyond initial investigator-assessed, modified RECIST 1.1 defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

7.2.4.2. Discontinuation from Study

Reasons for patient removal from the study include:

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

7.2.5. Completion of Study

It is anticipated that the enrollment period will be approximately 54 months. All patients will be followed with regard to survival until death, discontinuation from study follow-up, or termination/completion of study. Patients who die or complete the study follow-up through study closure will be considered to have "completed" the study.

The study will be declared complete when sufficient data is obtained to conclude the study; this is estimated at approximately two years from the date when the last patient in the study discontinues study treatment. Premature termination of this study may occur because of a regulatory authority decision, drug safety issues, or at the discretion of Celldex. In addition, Celldex retains the right to discontinue development of glembatumumab vedotin or varlilumab at any time.

8. STUDY TREATMENT

[redacted]

[redacted]

8.3. Nivolumab

8.3.1. Description, Packaging, and Labeling

Nivolumab will be obtained from commercial supply and handled/stored in a fashion consistent with packet insert and institutional policies. The following sections are based on package insert (dated July 2017). However, investigators are responsible for referencing the complete and most current package insert for full guidance regarding potential toxicity and dosing of nivolumab.

Nivolumab is available as 40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial.

8.3.2. Storage and Handling

Nivolumab does not contain a preservative. Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in original package until time of use. Do not freeze or shake.

After preparation, store the nivolumab infusion either:

- At room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

8.3.3. Preparation and Administration

Preparation of the Dilution

Visually inspect nivolumab solution for particular matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at the end of infusion.

Glembatumumab vedotin and nivolumab will be administered as separate infusions when dosing occurs on the same day. Nivolumab should be the first infusion and glembatumumab vedotin administered at least 30 minutes later as the second infusion. Patients 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. For additional details on glembatumumab vedotin administration please see Section 8.1.3.

8.4. Pembrolizumab

8.4.1. Description, Packaging, and Labeling

Pembrolizumab will be obtained from commercial supply and handled/stored in a fashion consistent with packet insert and institutional policies. The following sections are based on package insert (dated July 2017). However, investigators are responsible for referencing the complete and most current package insert for full guidance regarding potential toxicity and dosing of pembrolizumab.

Pembrolizumab is available as 50 mg lyophilized powder in single-use vial for reconstitution and as 100 mg/4 mL (25 mg/mL) solution in single-use vials.

8.4.2. Storage and Handling

Pembrolizumab does not contain a preservative. Store the reconstituted and diluted solution from the pembrolizumab 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigeration, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigeration, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

8.4.3. Preparation and Administration

Preparation of the Dilution

Reconstitution of pembrolizumab for injection (lyophilized powder):

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for intravenous infusion:

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

- Dilute pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration.

- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.

- Discard any unused portion left in the vial.

Administration

Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, lo-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Glembatumumab vedotin and pembrolizumab will be administered as separate infusions when dosing occurs on the same day. Pembrolizumab should be the first infusion and glembatumumab vedotin administered at least 30 minutes later as the second infusion. Patients 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. For additional details on glembatumumab vedotin administration please see Section 8.1.3.

[redacted]

[redacted]

8.6. Dose Modifications

8.6.1. Glembatumumab vedotin

Glembatumumab vedotin dose reductions in individual patients for toxicity are permitted; intra-patient dose escalations are not. Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. A maximum of two dose reductions are allowed. If a patient requires more than two dose reductions, they should be discontinued from treatment.

Dose reduction levels are as follows:

- Starting dose: 1.9 mg/kg
- First dose reduction: 1.3 mg/kg
- Second dose reduction: 1.0 mg/kg

Patients experiencing the following require dose reduction:

- Grade 3 or 4 non-hematological drug-related toxicity not resolving to Grade 2 or less within 72 hours of initiation of supportive care. Exceptions to this criterion include alopecia and other toxicities of non-vital organs after discussion with the medical monitor
- Grade 4 neutropenia lasting > 5 days or associated with fever > 100.5˚F

- Grade 4 thrombocytopenia
- Patients that develop Grade 2 or 3 neuropathy will have dosing held until neuropathy improves to ≤ Grade 1, and will be restarted with a dose reduction. Patients with Grade 4 neuropathy should have treatment discontinued altogether.
- Other events that, in the opinion of the treating investigator, warrant dose modification

8.6.2. Varlilumab

Modifications to the administered dose of varlilumab is not allowed. Patients who experience an event determined to be a treatment-limiting toxicity (Section 8.7) will permanently discontinue study treatment, including glembatumumab vedotin, and not be replaced. If treatment-limiting toxicity occurs in >2 of the first 10 patients, or in >20% of patients thereafter, all further patients enrolled will receive a varlilumab starting dose of 0.3 mg/kg and ongoing patients will also receive any further dosing of varlilumab at 0.3 mg/kg. If additional treatment-limiting toxicity occurs in >20% of patients receiving varlilumab at 0.3 mg/kg, enrollment will be interrupted pending evaluation by Celldex and the investigators.

Adjustments to the dosing schedule (treatment delays, infusion interruptions and infusion rate adjustments) are allowed for treatment-related toxicity as follows:

- Prior to each varlilumab administration at Cycle 2 and beyond, patients must be receiving < 10 mg/day prednisone or equivalent for treatment of drug related toxicity, and all toxicity related to prior treatment (including laboratory abnormalities) must resolve to ≤ grade 1 with the following exceptions:
  - Subjects may resume treatment in the presence of grade 2 fatigue
  - Subjects who have not experienced a grade 3 drug-related skin AE may resume treatment in the presence of grade 2 skin toxicity
  - Subjects with baseline grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of grade 2 AST/ALT or total bilirubin
  - Grade 2 drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
  - Patients with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
  - Patients may continue treatment with ≥ grade 2 lymphopenia
  - Treatment may continue without interruption for lipase and/or amylase increase at the investigator's discretion if not associated with symptoms. Grade 4 increases should be discussed with the Celldex medical monitor.
- Treatment may be delayed for up to three weeks to the next planned administration to allow sufficient time for recovery from treatment-related toxicities. If a delay greater than six weeks is required, the Investigator should confer with Celldex to determine the appropriateness of continued treatment.

8.6.3. PD-1 Targeted Checkpoint Inhibitor

The PD-1 targeted CPI should be administered in accordance with institutional standard practice with reference to the manufacturer's package insert. Dosing of these CPIs should not be omitted or significantly delayed to accommodate other study treatments being administered in this study. In Cohorts 3 and 5, no more than 3 doses of nivolumab or 2 doses of pembrolizumab should be missed prior to initiation of glembatumumab vedotin therapy.

8.6.4. CDX-301

There will be no CDX-301 dose modifications. If discontinued, CDX-301 will not be reinstituted. CDX-301 should not be administered if marked leukocytosis, e.g., WBCs greater than 50,000 cells/mm^3, is observed. Any ≥ Grade 3 injection site reactions thought related to CDX-301 warrant discontinuation of CDX-301 treatment.

Doses missed for any reason should not be made up; the next CDX-301 dose should be administered as per the treatment plan.

8.7. Treatment-Limiting Toxicity (TLT)

Any potential TLT occurring at any time during patient treatment in Cohorts 2-5 will be reported to Celldex within 24 hours of the site's awareness of the occurrence of the event. Any patient who experiences a TLT thought related to varlilumab, the PD-1 targeted CPI, or CDX-301 must discontinue dosing of the suspect drug as dose reductions are not allowed. Glembatumumab vedotin-related toxicity, including TLT, may be managed in accordance with guidance for glembatumumab vedotin dose reductions. Patients who discontinue varlilumab, the PD-1 targeted CPI, or CDX-301 may continue glembatumumab vedotin as monotherapy at the investigator's discretion. Patients in Cohort 2 who discontinue glembatumumab vedotin should discontinue varlilumab. Patients in Cohorts 3 and 5 who discontinue glembatumumab vedotin should discontinue the study treatment phase and may continue the PD-1 targeted CPI as per standard of care during study follow up. Patients in Cohorts 4 and 5 who discontinue glembatumumab vedotin should discontinue CDX-301.

In Cohort 2,

- All Grade 5 AEs attributed to study treatment **will** be considered TLTs.
- ALT of >3 x upper limit of normal (ULN) with a concurrent total bilirubin (TBL) >2 x ULN **will** be considered a TLT if no other reason can be found to explain the combination of increased aminotransferase (AT) and serum TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
- Any Grade 4 AEs attributed to study treatment will be considered TLTs, and any Grade 3 AEs attributed to study treatment will be evaluated by Celldex in collaboration with the investigators as potential TLTs, with the following exceptions (which do not need to be reported within 24 hours as potential TLT):
    - Lymphopenia or any increases in amylase and/or lipase not associated with clinically significant symptoms

- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement.
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
- Grade 3 infusion reaction that resolves within 6 hours to ≤ Grade 1.
- Grade 3-4 AEs expected as a result of glembatumumab vedotin therapy, (e.g., rash, neuropathy, neutropenia[#]) and not thought to be worsened by the addition of varlilumab will not be considered a TLT; such events should be managed in accordance with guidance for glembatumumab vedotin dose reductions. The overall incidence of study treatment discontinuation due to glembatumumab vedotin-related toxicity will be monitored on an ongoing basis by Celldex and the investigators.

[#]Investigators are referred to the table entitled "Adverse Drug Reactions (ADR) Observed with Glembatumumab Vedotin (Phase II Dose: 1.88 mg/kg, I.V., q3w) in Section 6 of the glembatumumab vedotin investigator's brochure; this table summarizes the adverse drug reactions/expected adverse events considered by Celldex to be causally related to glembatumumab vedotin based on clinical experience.

For Cohorts 3-5, any treatment-related toxicity that warrants discontinuation of the PD-1 targeted CPI, CDX-301, or glembatumumab vedotin will be considered a TLT.

8.8. Potential Toxicity and Management of Toxicity

Potential toxicity and guidance for the management of toxicity is summarized below. However, the glembatumumab vedotin, varlilumab, and CDX-301 Investigator's Brochures, and the PD-1 targeted CPI package insert, are the Single Reference Safety Documents that provides complete and relevant information about the known safety profile of each agent. Updates to these data will be provided as revisions to the Investigator's Brochures and through Investigational New Drug (IND) Safety Reports submitted to the investigator by Celldex, rather than by amendment to this section of the protocol.

Glembatumumab vedotin-related toxicities observed in previous studies have included neutropenia, alopecia, rash, pruritus, diarrhea, nausea, vomiting, constipation, fatigue/asthenia, pyrexia, anorexia, neuropathy and dysgeusia. Serious hematologic, gastrointestinal and dermatologic toxicity have occurred in 3-4% of treated patients. Infrequent but serious events have included fatal cases of toxic epidermal necrolysis and renal failure; severe or fatal sepsis (some cases were associated with pneumonia or urinary tract infection); and infusion site extravasation.

Toxicity related to varlilumab has been generally low-grade, and has included fatigue, arthralgia, nausea, decreased appetite, diarrhea, headache, vomiting, pyrexia, rash, pruritus, cough and neuropathy. Asymptomatic laboratory changes including lymphopenia, changes in liver function tests, and increases in lipase and amylase have occurred. Additional events consistent with an immune-mediated mechanism, such as hyperthyroidism, hypothyroidism, colitis, and infusion reaction, have been infrequently reported.

CDX-301 was generally well-tolerated in all prior studies. In the Celldex-sponsored phase 1 study in 30 healthy volunteers, treatment-related toxicity was infrequent, and reported only at the 25 and 75 µg/kg/day dose levels. One Grade 3 event, community acquired pneumonia, was considered treatment-related. No additional infections, DLT, treatment-related SAE, or treatment-related Grade 3 toxicity were reported. All other treatment-related adverse events were Grade 1 and included lymphadenopathy, diarrhea, injection site erythema, folliculitis, and dry mouth.

Investigators should be cognizant of the potential for unpredicted acute and chronic toxicity associated with the combination of glembatumumab vedotin and immunotherapy. Patients receiving glembatumumab vedotin and immunotherapy should be closely monitored for toxicity. Patients should be advised to immediately report symptoms such as unexplained abdominal pain, diarrhea, nausea or vomiting, severe rash, vision changes or signs of a potential infection, such as a fever of 100.5°F or greater, chills, cough, or pain on urination. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. Visual complaints should be investigated by an ophthalmologist. Laboratory tests must be performed as outline in Schedule of Assessments and results reviewed prior to dosing. 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 Cohorts 2-5 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. In Cohorts 4 and 5, patients should also be observed for at least 2 hours after the first dose of CDX-301, the first dose of glembatumumab vedotin, and for at least 1 hour at all other 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.

Toxicity should be aggressively worked-up and appropriately managed per the guidelines provided in the Glembatumumab Vedotin Investigator's Brochure, the Varlilumab Investigator's Brochure, the package insert for the PD-1 targeted checkpoint inhibitor, and the CDX-301 Investigator's Brochure to include the following:

- Pruritus and dry skin may be managed with emollients. Antihistamines may be used for pruritus as indicated. Less extensive rash may be treated with topical corticosteroids and more extensive/severe rashes may be treated with systemic corticosteroids. Possible preventative measures include the maintenance of clean and dry skin in folds under the breast, axillae, and groin. Patients should be counseled regarding the potential for alopecia. Sites are encouraged to collect photographic records of rashes for the medical record and dermatological consults as needed; biopsy collection and quantitation of gpNMB by the central laboratory is strongly encouraged.

- Early and aggressive management of all infections, particularly pneumonias and urinary tract infections is recommended, including the use of G-CSF and empiric antibiotic according to NCCN guidelines. The use of prophylactic antibiotics should be considered for patients with potential immune suppression (e.g., those requiring corticosteroids or other immunosuppressive agents [excluding patients in Cohort 2 who are subject to exclusion criteria #20]). Baseline risk factors such as prior chemotherapy and radiation,

tumor burden, performance status, and concomitant use of steroids should be evaluated and early sign of infections and fever should be closely monitored.

- Patients with neutropenia should be treated with standard supportive care

- Patients may receive antiemetic prophylaxis according to American Society of Clinical Oncology (Robert, Thomas et al.) guidelines (Kris, Hesketh et al. 2006) or local institutional standards. All patients should be treated for diarrhea or constipation with standard measures, as indicated.

- Acetaminophen may be used to manage drug-related adverse events such as fever, myalgias or arthralgias. Steroids may be used to manage more severe toxicity.

- Medication to treat anaphylactic or anaphylactoid reactions should be readily available at the time of the study drug infusion. Patients who do experience an infusion reaction may be pre-medicated with antihistamines, acetaminophen/paracetamol and/or corticosteroids prior to subsequent infusions. Patients who experience a Grade 4 infusion reaction should discontinue study treatment. Further guidance for management of infusion reactions is provided in the varlilumab Investigators Brochure, and may be modified based on local treatment standards and guidelines, as appropriate.

- Detailed guidance for management of immune-mediated adverse events (irAEs) are provided in the varlilumab Investigators Brochure.

- Detailed guidance for management of irAEs following nivolumab treatment are provided in the package insert. Management of such include administration of corticosteroids based on the severity of the reaction. In addition, nivolumab treatment should be withheld for: moderate immune-mediated pneumonitis, hepatitis, adrenal insufficiency, nephritis, or renal dysfunction; moderate or severe immune-mediated colitis, hypophysitis, or new-onset neurological signs or symptoms; severe immune-mediated hyperglycemia or rash. If any of these events increase in severity or become life-threatening, or if immune-mediated encephalitis or severe infusion reaction occurs, then nivolumab treatment should be permanently discontinued. Manage changes in thyroid function with initiation of thyroid hormone replacement as needed (nivolumab package insert, July 2017).

- Detailed guidance for management of irAEs following pembrolizumab treatment are provided in the package insert. Management of such include administration of corticosteroids based on the severity of the reaction. Changes in liver enzyme elevations due to immune-mediated hepatitis should be monitored, with treatment withheld or discontinued based on severity. In addition, pembrolizumab treatment should be withheld for: moderate immune-mediated pneumonitis, nephritis, or hypophysitis; moderate or severe colitis; severe hyperglycemia or hyperthyroidism. If any of these events increase in severity or become life-threatening, or if severe or life-threatening infusion reaction or skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur, then nivolumab treatment should be permanently discontinued. Manage changes in thyroid function with initiation of thyroid hormone replacement as needed (pembrolizumab package insert, July 2017).

- Leukocytosis, especially monocytosis, is expected during administration of CDX-301 and may be particularly pronounced when combined with other hematopoietic growth factors. Hematological parameters, including WBC and differential, should be monitored in subjects receiving CDX-301. CDX-301 should not be administered if marked leukocytosis, e.g. WBCs greater than 50,000 cells/mm^3, is observed.

- Pre-medication with diphenhydramine has been reported effective in the prevention of pruritic and erythemic reactions (Morse, Nair et al. 2000), and may be considered for patients who experience local reactions after treatment with CDX-301. Injection site reactions may also be treated with analgesics.

8.9. Accountability

Glembatumumab vedotin, varlilumab, and CDX-301 will be supplied by Celldex as open-label stock. The investigational product is to be used only for this protocol and not for any other purpose, and must be kept in an appropriate, secure area (e.g., locked refrigerator/cabinet) and stored in accordance with the conditions specified in this protocol/on the labels.

The investigator will assume responsibility for administration and dispensation of study medication. An accurate record of all study drugs received, dispensed, returned, and destroyed must be maintained. Drug supplies will be inventoried and accounted for throughout the study, and accountability records must be available for inspection at any time and provided to Celldex upon the completion of the study.

Upon receipt of any investigational product, an inventory must be conducted to confirm the quantity and condition of material received, and verification of receipt must be completed and returned in accordance with instructions provided by Celldex.

Re-supply of study medication may be requested in accordance with instructions provided by Celldex. Used, partly used and/or remaining unused investigational product will be either returned to Celldex or destroyed according to the site's Standard Operating Procedures (SOPs), as directed by Celldex, and a record of this disposition will be maintained.

The PD-1 targeted CPI will be obtained by each study site as commercial supply and handled/stored in a fashion consistent with package insert and institutional policies.

8.10. Compliance

Glembatumumab vedotin, varlilumab, the PD-1 targeted checkpoint inhibitor, and CDX-301 will always be administered by study staff at the clinic.

9. CONCOMITANT THERAPY

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

Subjects may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. During study treatment, patients may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management. Anti-emetics and steroids, if needed, for chemotherapy premedication are also permitted.

Growth factor support is permitted and should be administered with consideration to the American Society of Clinical Oncology (Robert, Thomas et al.) guideline on the use of hematopoietic colony-stimulating factors (Smith, Khatcheressian et al. 2006). If growth factor support for neutropenia is required while the patient is also being treated with CDX-301 (Cohorts 4 and 5), then white blood cell counts and differentials should be closely followed.

Efforts should be made to maintain stable doses of concomitant medications during the course of treatment with glembatumumab vedotin, varlilumab, the PD-1 targeted checkpoint inhibitor, and CDX-301.

If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously non-resectable tumor), these interventions are permitted, but should be avoided if clinically feasible until after the 12 week response assessment. A tumor response assessment should be conducted prior to any intervention, in order to document progression and/or confirm an objective response. Patients who undergo surgical resection or radiation in the absence of progression may continue to receive study treatment until remaining lesions meet criteria for progression of disease.

All concomitant medication will be documented in the CRF if taken within 28 days prior to initiation of study treatment, and either (whichever occurs sooner): 1) 28 days after last dose of study treatment (glembatumumab vedotin), or 70 days after last dose varlilumab (the latter whichever occurs later in Cohort 2), or 70 days after last dose of the PD-1 targeted checkpoint inhibitor (the latter whichever occurs later in Cohort 3); or 2) initiation of alternate anti-cancer therapy. In addition, all anti-cancer medications should be recorded throughout the duration of study follow-up.

9.1. Glembatumumab vedotin

The effect of glembatumumab vedotin on the absorption, metabolism, or excretion of other drugs has not been studied. Drugs known to strongly inhibit CYP3A4 should be used with caution, and drugs known to be potent CYP3A4 inducers should be avoided, if at all possible, while patients are exposed to glembatumumab vedotin. (See Section 8.8 for further information.) A table listing P450 enzyme-drug interactions is available at: http://medicine.iupui.edu/clinpharm/ddis/main-table).

Prolonged use of systemic corticosteroids above the physiologic dose (5 mg prednisone or equivalent) should be avoided during the study as this may increase the risk of infection and sepsis (see Section 8.8).

9.2. Varlilumab

Any vaccination containing live, attenuated, or inactivated virus may be permitted if clinically indicated. However, this must be discussed with the Celldex Medical Monitor prior to

administration and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination is permitted on study without restriction.

Immunosuppressive agents are prohibited during the study, with the following exceptions:

- Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating adverse events. Patients receiving corticosteroids for treatment of drug-related adverse events must be at ≤ 10 mg/day prednisone or equivalent prior to re-initiation of study therapy
- Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

Pre-medication as prophylaxis for infusion reaction should only be initiated if clinically indicated.

9.3. PD-1 Targeted Checkpoint Inhibitor

The manufacturer's package insert for the PD-1 targeted checkpoint inhibitor should be consulted for guidance on concomitant medications and any known or theoretical risks.

9.4. CDX-301

The effect of CDX-301 on the absorption, metabolism, or excretion of other drugs has not been studied. Initiation of any new medication during the course of the study treatment is discouraged and should only be done for a medically indicated adverse event or new condition. Any vaccination is prohibited until at least 28 days after the last dose of CDX-301. If growth factor support for neutropenia is required while the patient is also being treated with CDX-301 (Cohorts 4 and 5), then white blood cell counts and differentials should be closely followed.

10. STUDY PROCEDURES

10.1. Schedule of Investigations and Data Collection

The study is divided into phases with associated evaluations and procedures that must be performed at specific time points, as described in the following sections. The Study Assessment Schedule (Table 1 and Table 2) summarizes the frequency and timing of various efficacy, safety, and other measurements.

10.1.1. Screening Period

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

The assessments outlined for the Screening Visit in the Study Assessment Schedule (Table 1 and Table 2) will be completed for each patient prior to inclusion in the study, and results will be evaluated to verify entry criteria prior to study enrollment.

10.1.2. Study Enrollment

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

Enrollment should occur in accordance with instructions provided by Celldex, only after confirming all inclusion criteria and none of the exclusion criteria have been met. Following the completion of Cohort 4, there will be an evaluation period whereby the Sponsor and the investigators will assess the safety and activity of both Cohorts 3 and 4. If the results are supportive, then enrollment in Cohort 5 will be initiated.

10.1.3. Treatment Phase

Specific procedures to be performed at each visit during the treatment phase are illustrated in the Study Assessment Schedule (Table 1 and Table 2).

The End of Treatment Visit should be performed within 28 days after last study drug dosing and prior to initiation of alternate therapies. As described in Section 10.2.2.3, any abnormalities (adverse events) attributed to study drug dosing, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

10.1.4. Disease Assessment Visits

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. 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.

10.1.5. Survival Follow-up

Subsequent to progression of disease, all patients will be followed at 12 week intervals until study closure.

10.2. Methods of Assessment

10.2.1. Activity

10.2.1.1. Anti-tumor Activity

Anti-tumor activity will be assessed via ORR, PFS, DOR and OS. Tumor response and progression will be defined by the investigator according to RECIST 1.1 criteria. In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an IRC, blinded to investigator assessments. For Cohorts 2-5, supplementary retrospective analyses of tumor response and progression may also be

performed using irRECIST criteria (in which new lesions do not constitute progression, but contribute to the calculated sum of diameter of all measurable disease).

10.2.1.2. Immunogenicity

Patients will be monitored for the development of anti-glembatumumab vedotin and anti-CR011 antibodies. In addition, patients in Cohort 2 will be monitored for anti-varlilumab antibodies, and patients in Cohorts 4 and 5 will be monitored for anti-CDX-301 antibodies. Additional analyses will assess whether these antibodies are neutralizing.

10.2.1.3. Pharmacokinetic Evaluations

Concentration of the glembatumumab vedotin ADC, TA, and free MMAE (Cohorts 1-5), varlilumab (Cohort 2), and CDX-301 (Cohorts 4 and 5) will be determined using GLP compliant ELISA and LC-MS/MS methods. The impact of circulating gpNMB levels or other soluble mediators on glembatumumab vedotin pharmacokinetic parameters may also be examined.

10.2.1.4. Pharmacodynamics

Pharmacodynamic parameters will be evaluated via assessment of post-treatment tumor tissue obtained via voluntary biopsy or resection (Cohorts 1-3), mandatory pre-study and on-treatment biopsies (Cohorts 4 and 5), and blood samples. Parameters evaluated may include localization of glembatumumab vedotin, CR011, or MMAE at the tumor site and/or gpNMB expression levels in serum and tumor tissue, as well as evaluation of other soluble mediators, tumor infiltrating and peripheral leukocytes, circulating tumor cells and other immune response cells of interest such as gpNMB-expressing myeloid-derived suppressor cells, and the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations. (Cohorts 4 and 5). Additional analysis may include immune response assessment to potentially relevant tumor antigens.

10.2.2. Safety Variables

10.2.2.1. Adverse Events: Definition

An adverse event is any untoward medical occurrence in a patient administered a study treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. All observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be reported, as described in the following sections. For the purposes of this current study, "study treatment" is defined as glembatumumab vedotin and/or: varlilumab, nivolumab, pembrolizumab, or CDX-301.

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

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

- severity of the event: adverse event severity will be primarily assessed using NCI Common Terminology Criteria for Adverse Events v4.0. (NCI-CTCAE), Version 4.0, division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (Robert, Thomas et al.), National Institute of Health (NIH), Department of Health and Human Services (DHHS) published May 29, 2009 at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
- onset/resolution dates and outcome
- causality: the relationship of each adverse event to study drug will be defined as "unrelated" or "related" to study treatment:
    - Unrelated: There is little or no possibility that the study drug caused the reported adverse event; and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications appear to explain the adverse event.
    - Related: there exists at least a reasonable possibility that the study treatments caused or contributed to the adverse event; an inability to identify an alternate etiology for an adverse event should not, by itself, justify a "related" attribution.
- whether it meets the criteria for classification as a serious adverse event (see Section 10.2.2.2)

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

- Progression of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for a serious adverse event. If there is any uncertainty about a finding or event being due solely to progression of neoplasia, the finding or event should be reported as an adverse event or serious adverse event as appropriate. Death due to disease progression occurring within 28 days of study treatment should be reported to Celldex within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a serious adverse event.
- Withdrawal due to an adverse event should be distinguished from withdrawal due to insufficient response, and recorded on the appropriate adverse event CRF page. For example, if an AE due to recurrence/progression of disease necessitates discontinuation from the study, the primary reason for study discontinuation should be recorded as "Recurrence/Progression of Disease" (not Adverse Event).
- Abnormal objective test findings should be reported as adverse events if the findings are associated with accompanying symptoms, require additional diagnostic testing or medical/surgical intervention, lead to dose modification/discontinuation of study treatment and/or are considered otherwise clinically significant.
- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For

example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

- Any AEs/SAEs resulting in death should be recorded with an end date equal to the death date, while other events ongoing at the time of death should be recorded with an outcome of "continuing". If requested, a summary of available autopsy findings should be submitted as soon as possible to Celldex.

10.2.2.2. Serious Adverse Events (SAEs): Definition

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

- Death (any AE that has a fatal outcome must be assigned NCI-CTCAE Grade 5)
- Requires initial or prolonged inpatient hospitalization exceeding 24 hours. As well, any event occurring while the patient is hospitalized which would otherwise require hospitalization or requires transfer within the hospital to an acute/intensive care unit should also be reported under this criterion. This criterion would exclude hospitalization in the absence of a precipitating adverse event, such as admission for treatment of a preexisting condition not associated with a new/worsening adverse event, or admission for elective surgery. As well, admission to rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries are not considered "hospitalizations" for the purpose of this criterion.)
- Is life-threatening (An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
- Is a persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other significant medical hazard (Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

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

- Progression of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for a serious adverse event. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should

be reported as an adverse event or serious adverse event as appropriate. Death due to disease progression occurring within 28 days of study treatment should be reported to Celldex within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a serious adverse event.

10.2.2.3. AE/SAE Reporting

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

AEs and SAEs should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through (whichever occurs first) either: a) 28 calendar days after the last administration of glembatumumab vedotin or 70 calendar days after the last administration of varlilumab (the latter whichever occurs later, Cohort 2); 70 days after last dose of the PD-1 targeted checkpoint inhibitor (the latter whichever occurs later in Cohorts 3 and 5); 28 calendar days after the last administration of CDX-301 (the latter whichever occurs later, Cohorts 4 and 5); or b) initiation of alternate anticancer therapy.

However:

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

All AEs will be reported on the AE page(s) of the CRF, while SAEs will also be reported in an expedited fashion using the SAE Report. The AE CRFs and SAE Reports must be completed in a consistent manner; for example, the same AE term, causality, severity, and onset/resolution dates should be used on both forms.

In case of an SAE (regardless of causality), an SAE Report must be completed and submitted to Celldex within 24 hours of the site's notification of the event, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. The investigator is obligated to pursue additional information required for thorough evaluation of each SAE as may be requested by Celldex.

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

10.2.2.4. Rapid Notification of Adverse Events of Interest

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events, even if the nature of the adverse event is not deemed serious:

- Any potential treatment-limiting toxicity in Cohorts 2-5 (See Section 8.7)
- Death due to disease progression, if occurring within 28 days of study treatment
- Any overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important).
- If a female becomes, or is found to be, pregnant within 6 months of exposure to the study treatments (maternal exposure) or if a male has been exposed to the study treatments within 6 months prior to conception (paternal exposure). Any follow-up to the above-referenced events, including outcome of pregnancy. Further follow-up of birth outcomes will be handled on a case-by-case basis. In the case of paternal exposure, the investigator must obtain permission from the patient's partner in order to conduct any follow-up or collect any information.

Given the expected mechanism of action of varlilumab, the PD-1 targeted CPI, and CDX-301, particular attention will be given to adverse events in Cohorts 2-5 that may be secondary to activation of the immune system and have been observed with other immune-stimulatory antibodies; such events include diarrhea/colitis, rash, endocrinopathies, and hepatitis (see Section 8.8).

10.2.2.5. Laboratory Safety Data

The following clinical laboratory tests will be performed during this study to assess safety (see Table 1 and Table 2 for specific tests):

- Hematology
- Serum Chemistries
- Urinalysis

Investigators must document their review of each laboratory report by signing or initialing and dating each report, as well as addressing the clinical significance and causality (for significant abnormalities). Section 10.2.2.1 provides further guidance as to when abnormal laboratory results are to be reported as adverse events.

10.2.2.6. Other Safety Data

The following evaluations will also be performed during the study to measure the safety and tolerability of glembatumumab vedotin as monotherapy and in combination with varlilumab:

- Vital sign measurements
- Physical examination
- ECGs
- ECOG performance status (Appendix 4)

11. STATISTICAL CONSIDERATIONS

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

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

All statistical analyses will be performed separately for the five treatment cohorts, unless specified differently. Given the timing of different cohorts, statistical analyses will be performed for each cohort when sufficient data is available upon completion of enrollment.

11.1. Analysis Endpoints

Efficacy, Primary

- Objective response rate (ORR) *(Cohorts 1-3, 5)*

Efficacy, Secondary

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- ORR *(Cohort 4)*

Efficacy, Exploratory

- Immune-related RECIST ORR and PFS *(Cohorts 2-5)*

Safety

- 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

Correlative

- Concentration of ADC, TA, and free 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, other immune response cells of interest, and the effect

of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations (Cohorts 4 and 5). Additional analysis may include immune response assessment to potentially relevant tumor antigens.

11.2. Sample Size and Power Calculation

Five cohorts of patients will be studied. In Cohort 1, approximately 52 evaluable patients may be enrolled and treated with glembatumumab vedotin monotherapy with ORR as the primary endpoint. As patients who discontinue study prior to the first disease assessment for reasons unrelated to study treatment will be excluded from the response-evaluable population, it is anticipated that approximately 60 patients will be enrolled.

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 evaluable patients will help 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, 3, and 5, approximately 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%, 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 bionomial test. Cohort 4 will enroll approximately 10-12 patients for safety and tolerability assessment of glembatumumab vedotin and CDX-301. Pre-study and on-treatment tumor biopsies will be analyzed for the effect of CDX-301 on the tumor microenvironment, including the effect on intratumoral dendritic cell populations. The anti-tumor activity will also be explored as a secondary endpoint.

Patients in Cohorts 2-5 who experience an event determined to be a treatment-limiting toxicity will not be replaced and will be considered evaluable.

11.3. Interim Analysis

No interim analysis is planned.

11.4. Analysis Populations

11.4.1. Efficacy Analysis

The five treatment cohorts will be analyzed separately. For each cohort, the response-evaluable population will be the basis for the primary analysis of ORR in this study. 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. Every effort will be made to ascertain outcomes for all enrolled patients, irrespective of early discontinuation of protocol therapy.

The Intention-to-Treat (ITT) population constitutes all treated patients and will be used for secondary analyses of ORR and all other endpoints.

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

11.4.2. Safety Analysis

The safety population will include all patients who receive at least one dose of protocol treatment. 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.

11.5. Statistical Methods

For the analyses described below, the most recent tumor sample collected prior to study entry 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 or Pre-Study and On-Treatment samples to determine whether gpNMB expression changes over time and/or with specific prior therapies.

All statistical analyses will be performed separately for the five treatment cohorts, unless specified differently. Given the timing of different cohorts, statistical analyses will be performed for each cohort when sufficient data is available upon completion of enrollment.

11.5.1. Efficacy Analysis

Objective Response Rate

ORR will be estimated as the proportion of patients who achieve best overall response of CR or PR per RECIST 1.1 that are confirmed at an interval of at least 28 days. Secondary analyses of ORR will include responses observed at a single-time point. The final analysis of ORR will be based on the investigator assessment of response. However, in the event of a positive study outcome, an additional assessment of ORR may be performed by an IRC. The estimate of the

objective response rate will be accompanied by one- and two-sided exact 95% Clopper-Pearson confidence interval for each cohort. In addition, one-sample exact binomial test will be used to test the null hypotheses of ORR (Cohort 1: ORR≤5%; Cohorts 2, 3, and 5: ORR ≤5%, and ORR ≤10%) with one-sided significance level of 0.05 for Cohort 1 and 0.1 for Cohorts 2, 3, and 5. The primary ORR analyses will be based on respective evaluable population and the secondary analysis will be based on respective ITT population. In addition, supplementary analyses of tumor response and progression may also be performed using irRECIST criteria (in which new lesions do not constitute progression, but contribute to the calculated sum of diameter of all measurable disease). Exploratory analysis will be performed for comparing the three cohorts on efficacy endpoints, and no adjustment for multiple testing will be considered.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest diameters of target lesions. Based on the range of gpNMB expression, the correlation between gpNMB expression level and maximum decrease from baseline in the sum of longest diameters of target lesions will be evaluated. For this analysis all available patients 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.

Duration of Response

DOR will be calculated for the ITT population who achieve CR or PR. For such patients, DOR is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that recurrent or progressive disease is objectively documented. In such cases, recurrent or progressive disease will be assessed relative to the smallest tumor burden measurements recorded since the start of protocol treatment.

DOR will be summarized descriptively using the Kaplan-Meier method. DOR will be right-censored for patients who achieve CR or PR based on the conventions described for PFS.

Progression-free Survival

PFS is defined as the number of months from the start date of protocol treatment to the earlier of disease progression or death due to any cause. Disease progression will be assessed using RECIST 1.1 and irRECIST for cohort 2. PFS will be based on the ITT patient population.

PFS will be right-censored for patients who met one or more of the following conditions:

- Patients with no baseline or post-baseline disease assessments unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event)
- Patients who initiate subsequent anti-cancer therapy in the absence of documented progression
- Patients who die or have disease progression after missing two or more consecutively scheduled disease assessment visits

- Patients who are last known to be alive and progression-free on or before the data cut-off date

The progression and censoring dates will be based on the conventions described in the May 2007 FDA Guidance for Industry, '*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*'. The primary analysis of PFS will be based on PFS events determined by the investigator. In addition, in the event of a positive study outcome, an additional assessment of tumor response and progression may be performed by an IRC blinded to investigator assessments.

PFS will be summarized descriptively using the Kaplan-Meier method. Median PFS and its corresponding 95% confidence interval will be reported. The PFS rate and its corresponding 95% confidence interval for at various landmark time points will also 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 95% confidence interval. Similar analyses may be performed for additional landmarks.

If feasible based on the range of gpNMB expression levels, the association between gpNMB expression level and PFS will be evaluated using a Cox proportional hazards model. For this analysis, patients with gpNMB expression measured on a continuous scale (percentage of gpNMB-positive tumor cells) will be analyzed. When a factor is continuous, the hazard ratio is interpreted as the change in risk for each 1-unit increase in the factor. For example, a hazard ratio of 0.99 indicates the hazard for the event decreases by 1% for each 1%-unit increase in gpNMB expression level. For Cohort 1, if a true hazard ratio of 0.99 is assumed and the standard deviation for gpNMB expression level is ± 35%, 36 PFS events from among the 52 evaluable patients (70% event rate) will provide approximately 80% power with one-sided significance level of 10% (Hsieh and Lavori 2000). The predictive power of various cut-off values for gpNMB expression will be explored based on a receiver operating curve (ROC) analysis for censored data (Gönen and SAS Institute. 2007). Similar analyses will be performed for Cohorts 2 and 3 separately.

Overall Survival

OS is defined as the number of months elapsed between the start date of protocol treatment and the date of death (whatever the cause). OS will be based on the ITT population. Patients who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact or data analysis cutoff date, whichever event occurs first. The duration of 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 reverse Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

11.5.2. Protocol Therapy and Concomitant Medications

The total number of doses and total dose administered will be tabulated by cohort. The primary reason for treatment delays, dose reductions and permanent discontinuation of protocol treatment will be tabulated in a similar manner.

Concomitant medications will be coded using WHO Drug Dictionary. All medication data will be listed individually and summarized by anatomical therapeutic class and preferred name.

11.5.3. Safety Analysis

Safety and tolerability will be assessed by incidence, severity, and changes from baseline of all relevant parameters including AEs, vital signs, and laboratory values.

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing one or more AEs will be summarized by relationship to study drug, and severity. Treatment-emergent AEs are defined as AEs that start on or after the first day study drug is administered. AEs will be summarized by the number and percentage of patients who experienced the event, according to system organ class and preferred term. A patient reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term. Unless specified otherwise, the denominator for these calculations will be based on the number of patients who receive at least one dose of study drug, irrespective of the total number of doses administered. AEs will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. Additional summaries may also be provided for SAEs and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual patient data listings.

Vital sign and laboratory results will be summarized descriptively. The incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided. The use of red blood cell and other blood component transfusions and/or growth factor support will be reported. Similar analyses will be done for selected chemistry tests (including liver and renal function tests). Data listings of all vital sign and laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in data listings and will include flags for high and low values.

12. DATA HANDLING AND RECORD KEEPING

12.1. Data Quality Assurance

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

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

Celldex will provide Case Report Forms (CRFs) for the recording and collection of data. The CRF will either be in paper or via an electronic data capture (EDC) system. Entries made in the CRF must be either verifiable against source documents, or have been directly entered into

the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. Corrections to CRFs and source data will be made only by authorized members of the study staff, clearly entered, initialed and dated. The investigator will sign the CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will be made aware of the corrections and his/her approval will be documented by re-signing. In cases where an EDC system is utilized, an electronic audit trail is maintained with similar information collected.

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

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

12.2. Archiving of Study Documentation

To enable evaluations and/or audits by regulatory authorities or Celldex, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records); all original signed informed consent forms; copies of all CRFs; serious adverse event forms; source documents and detailed records of treatment disposition; and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The duration of record retention by the investigator should be according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

13. ETHICAL CONSIDERATIONS

13.1. Independent Ethics Committee or Institutional Review Board

International Conference on Harmonization (ICH) GCP guidelines require that all investigational drug studies be conducted under the auspices of an Institution Review Board/Ethics Committee (IRB/EC). This committee, the makeup of which must conform to federal, state, and local guidelines regarding such, will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent. The investigator will provide Celldex with a copy of the communication from the IRB/EC to the investigator indicating approval/favorable opinion of

the protocol and consent form. All changes to the protocol or consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients.

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

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

13.2. Ethical Conduct of the Study

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

13.3. Patient Information and Informed Consent

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

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

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

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

13.4. Protocol Amendments

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

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

13.5. Confidentiality

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

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

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

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

14. PUBLICATION POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of Celldex, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Celldex supports publication of the results of this trial in appropriate scientific journals and meetings. In accord with standard editorial and ethical practice, Celldex encourages

publication of multicenter trials only in their entirety and not as individual center data. Any presentation or publication of data collected from this study will be generated in accordance with the following principles:

- Authorship (including identification of a lead author and corresponding author) will be determined by mutual agreement in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, according to overall contribution to study conduct, chiefly by leadership in study design and decision making, and then by contribution. All meaningful contributions will be acknowledged.

- Authors will follow Good Publication Practice (GPP) and other recognized standards and will work together to: discuss practical considerations (e.g., choice of potential journals or congresses); avoid duplicate publication; ensure that publications are accurate, balanced, transparent and produced in a timely manner; assume responsibility for the content, accuracy and completeness of the publication; establish a process based on honest scientific debate to resolve differences in interpretation of data; disclose all potential conflicts of interest; disclose funding sources including Celldex support for the study (funding and in-kind support such as medical writing); and assume responsibility for all final decisions on publication content and for final approval of the version for submission or presentation.

- Celldex will provide authors with access to all relevant study documents needed to support the publication, including protocols, statistical analysis plans, clinical study reports (when available), and data tables; describe editorial and other support that may be available to the authors for the development of a publication and ensure that all authors agree to any support to be provided; and provide a timely review of the publication or presentation.

- Additionally, authors and Celldex will avoid premature release of study information that could jeopardize publication and respect embargoes set by journals and congresses.

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Appendix 1: Approval Signature

Approval Signature
Protocol CDX011-05

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 2: Investigator Signature

Investigator Signature

Protocol CDX011-05

I confirm that I have read this protocol, I understand it, and I will work according to this protocol, the applicable ICH guidelines for good clinical practices, and the applicable laws and regulations of the country of the study site for which I am responsible. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in the protocol and my agreement with Celldex Therapeutics, Inc. I will promptly submit the protocol to applicable ethical review board(s) and will not begin the study until regulatory approval has been obtained.

Instructions to the Investigator: Please SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed page to Celldex Therapeutics, Inc., and retain a photocopy with this protocol.

Signature of Investigator	Date
Investigator Name (Please Print)	Investigator Title
Name of Facility	Location of Facility [City, State (if applicable), Country]

Appendix 3: RECIST 1.1 Criteria

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

Only patients with measurable disease on baseline evaluations should be included in Protocol CDX011-05. Measurable disease is defined by the presence of at least one measurable lesion (see "Measurability of Tumor at Baseline" below). At baseline, lesions should be identified as either "Target" or "Non-Target" as follows:

Target Lesions:

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

Non-Target Lesions:

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

MEASURABILITY OF TUMOR AT BASELINE

- Measurable: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
  - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20mm by chest X-ray.

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

Special considerations regarding lesion measurability:

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

METHODS OF LESION MEASUREMENT

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

TUMOR RESPONSE EVALUATION

Evaluation of target lesions:

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

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive *Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

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

Evaluation of non-target lesions:

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

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

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

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

New lesions:

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

- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered that reveals

metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

Evaluation of overall response:

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

Appendix 3 Table 1. Schedule of Assessments provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore, non-target) disease only, Appendix 3 Table 2. Outcomes for Metastatic or Locally Advanced Melanoma Patients Treated with Approved Targeted Therapies is to be used.

Special notes on evaluation of overall response:

- Missing assessments and inevaluable designation:
  - When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
  - If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.
- 'Symptomatic deterioration': Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix 3 Table 1 and Appendix 3 Table 2.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.
- Confirmation of response: In the event of complete or partial responses, efforts should be made to obtain a confirmatory scan (no sooner than 28 days later).

Appendix 3 Table 1: Overall response: patients with target +/–non-target disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Appendix 3 Table 2: Overall response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

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

FREQUENTLY ASKED QUESTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Can PET–CT be used with RECIST?

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

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

Appendix 4: ECOG Performance Status

ECOG PERFORMANCE STATUS*

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

* As published in Am. J. Clin. Oncol (Oken, Creech et al. 1982)

Appendix 5: Cockroft and Gault Equation

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

Creatinine clearance for females = 0.85 x male value

Appendix 6: Approved and/or Investigational Immune-Directed and Molecularly Targeted Drugs used with Advanced Melanoma

Product Name	Mechanism of Action	Molecular Target
Approved Products		
IPILIMUMAB (Yervoy)	Checkpoint inhibitor	CTLA-4
NIVOLUMAB (Opdivo)	Checkpoint inhibitor	PD-1
PEMBROLIZUMAB (Keytruda)	Checkpoint inhibitor	PD-1
VEMURAFENIB (Zelboraf)	Kinase inhibitor	BRAF oncogene (V600E mutation)
DABRAFENIB (Tafinlar)	Kinase inhibitor	BRAF oncogene
TRAMETINIB (Mekinist)	Kinase inhibitor	MEK 1/2 (MAP-ERK signaling pathway)
SORAFENIB (Nexavar)	Kinase inhibitor	Multiple pathways including BRAF/MEK/ERK
Investigational Products		
ATEZOLIZUMAB (MPDL3280A)	Checkpoint inhibitor	PD-L1 (PD-1 ligand)
MDX-1105	Checkpoint inhibitor	PD-L1 (PD-1 ligand)
AMPLIMMUNE (AMP-224)	Checkpoint inhibitor	PD-1
LCX818	Kinase inhibitor	BRAF oncogene
MEK162	Kinase inhibitor	MEK 1/2 (MAP-ERK signaling pathway)
SELUMETINIB (AZD6244)	Kinase inhibitor	MEK 1/2 (MAP-ERK signaling pathway)
PIMASERTIB (MSC1936369B)	Kinase inhibitor	MEK 1/2 (MAP-ERK signaling pathway)

NB: Several additional investigational drugs are in early clinical development and are not listed here. Please check with the medical monitor and clinicaltrials.gov for further information on the mechanism of action of other investigative agents relevant for patients with advanced melanoma.

Appendix 7: Summary of Changes

The following changes have been made to Protocol CDX011-05 as Amendment 4:

SECTION(S)	CHANGE/RATIONALE

2 Glossary of Abbreviations
3 Synopsis
4 Schedule of Assessments
5.5 CDX-301
5.6 Study Rationale
6 Study Objectives
7 Investigational Plan
7.1 Overall Design and Plan of the Study
7.2 Number of Patients
7.2.2.1 Inclusion Criteria
7.2.2.2 Exclusion Criteria
7.2.4 Withdrawals and Replacement of Patients
7.2.5 Completion of Study
8 Study Treatment
8.5 CDX-301
8.6 Dose Modifications
8.6.4 CDX-301
8.7 Treatment-Limiting Toxicity
8.8 Potential Toxicity and Management of Toxicity
8.9 Accountability
8.10 Compliance
9 Concomitant Therapy
9.4 CDX-301
10 Study Procedures
10.1.2 Study Enrollment
10.2.1.2 Immunogenicity
10.2.1.3 Pharmacokinetic Evaluations
10.2.1.4 Pharmacodynamics
10.2.2.3 AE/SAE Reporting
10.2.2.4 Rapid Notification of Adverse Events of Interest
11 Statistical Considerations
11.1 Analysis Endpoints
11.2 Sample Size and Power Calculation
11.4.1 and 11.5.1 Efficacy Analysis
15 References
	Added Cohorts 4 and 5 for the combination of glembatumumab vedotin and CDX-301 +/- PD-1 targeted CPI based on the rationale that combining cytotoxic therapy with immunotherapy may induce an immune response and improve anti-tumor activity. These new cohorts result in the following changes:
	• Included CDX-301 as additional therapy
	• Increased the number of patients in study overall
	• Included CDX-301 +/- CPI in study objectives
	• Overview of study design
	• Added to TLT criteria
	• Revised eligibility criteria including:
	  ○ Inclusion #5c, added that all patients in cohorts 4 and 5 must submit a mandatory pre-entry and on-treatment biopsy until further data is not needed
	  ○ Exclusion #24, added window for vaccinations prior to study entry for cohorts 4 and 5
	• Criteria for evaluation includes CDX-301, Cohorts 4 and 5
	• Statistical methods
	• Section 4: new Table 2 on schedule of study procedures for Cohorts 4 and 5
	• Section 5.5: new section on CDX-301
	• Section 7.2.5: study completion revised to 54 months
	• Section 8.5: new section on CDX-301 drug product, storage, preparation and administration
	• Section 8.6.4: new section on CDX-301 dose modifications
	• Section 9.4: new section on CDX-301 concomitant therapy

3 Synopsis 7.1 Overall Design and Plan of the Study 7.2.4 Withdrawals and Replacement of Patients 11.4.1 Efficacy Analysis	Defined response-evaluable population for clarification
4 Schedule of Assessments, Tables 1 and 2, footnote 23 8.6.3 PD-1 Targeted Checkpoint Inhibitor	Allowed for up to 2-3 doses of missed CPI prior to study entry to enhance enrolled
5.2.3 Glembatumumab Vedotin: Clinical Summary	Updated number of patients treated
8.1.1 Description, Packaging, and Labeling	Added description of the drug product for reference
8.3 Nivolumab and 8.4 Pembrolizumab	Updated dates of the most recent package inserts
14 Publication Policy	Revised to include ICMJE criteria and GPP principles
Appendix 1 Approval Signature	Approver changed due to departure of CMO
Throughout	Typographical corrections and formatting adjustments

The following changes have been made to Protocol CDX011-05 as Amendment 3:

SECTION(S)	CHANGE/RATIONALE
Cover page 3 Synopsis 5 Background/Rationale 5.4 PD-1 Targeted Checkpoint Inhibitor 5.5.3 Rationale for Permitting Continued Treatment in Cases of Apparent Progressive Disease 6 Study Objectives 7 Investigational Plan 7.1 Overall Design and Plan of the Study 7.2 Number of Patients 7.2.2.1 Inclusion Criteria 7.2.2.2 Exclusion Criteria 7.2.4 Withdrawals and Replacement of Patients 7.2.5 Completion of Study 8 Study Treatment 8.5.3 PD-1 Targeted CPI 8.7 Potential Toxicity and Management of Toxicity 8.8 Accountability 10.2.2.3 AE/SAE Reporting 10.2.2.4 Rapid Notification of Adverse Events	Added Cohort 3 for the combination of glembatumumab vedotin and PD-1 targeted checkpoint inhibitor (CPI) based on the rationale that combining cytotoxic therapy with immunotherapy may induce an immune response and improved anti-tumor activity. This new cohort results in the following changes • Study title • Included nivolumab and pembrolizumab as additional therapies • Increased the number of patients in study overall • Included PD-1 targeted therapy in study objectives • Added treatment-limiting toxicity rule • Revised eligibility criteria: o Inclusion #3, added *"For Cohort 3, progression (confirmed from two scans at least 4 weeks apart) must have occurred during the PD-1 targeted CPI treatment and the investigator has deemed it appropriate to continue to treat beyond confirmed disease progression."* o Inclusion #4, added *"For Cohort 3, prior treatment received must include PD-1 targeted CPI (i.e., nivolumab or pembrolizumab) administered during the most recent disease progression and for patients with a BRAF mutation, at least one BRAF- or MEK-targeted therapy when appropriate."* o Inclusion #5, included skinfold biopsy for this cohort; for both cohorts 2 and 3 with the immunotherapy combination noted that the biopsy will be collected until further data is not needed to reduce patient burden o Inclusions #19-21, added new cohort 3 o Exclusion #3, noted that washout period for prior monoclonal antibodies does not apply since treatment with prior PD-1 targeted therapy should be continuous o Exclusions #22 and #23 added to exclude patients with interstitial lung disease and active diverticulitis for safety • Statistical methods • Section 5.4.1: new section of PD-1 pathway and inhibitors • Section 7.2.5: study completion updated to 36 months • Sections 8.3 and 8.4: new sections on nivolumab and pembrolizumab drug products, storage, preparation and administration • Section 8.5.3: new section on dose modification for PD-1 CPI
2 Glossary of Abbreviations 15 References	Included terms and references relevant to PD-1 CPI
3. Schedule of Assessments	Footnote 5: clarified that the scheduling of disease assessment visits is based on first dose of glembatumumab vedotin at C1D1 Footnote 18: noted that PBMC will be collected until sufficient data has been generated to minimize patient burden With addition of Cohort 3: • Table 1: included Cohort 3 in PBMC and PK collection • Footnote 3: included treatment of PD-1 CPI

	• Footnote 13: assessment of vital signs when PD-1 CPI is dosed • Footnote 19: PK analysis added which may be performed for each immunogenicity sample to interpret any negative immunogenicity results • Footnote 21: specified PD-1 CPI treatment, clinical visits and monitoring
5.2.3 Glembatumumab vedotin: Clinical Summary	Added interim summary of results from Cohort 1 from ESMO 2016 Congress presentation
10.2.2.2 Serious Adverse Events (SAEs): Definition	SAE definition updated to reflect Celldex core safety language for protocols based on FDA guidance
Synopsis, Statistical Methods 11 Statistical Considerations	Included analyses and methods for Cohort 3; number of patients
Throughout	Formatting modifications and typographical corrections

The following changes have been made to Protocol CDX011-05 as Amendment 2:

SECTION(S)	CHANGE/RATIONALE
Cover page 3 Synopsis 5 Background/Rationale 6 Study Objectives 7 Investigational Plan 7.1 Overall Design and Plan of the Study 7.2 Number of Patients 7.2.2.1 Inclusion Criteria 7.2.2.2 Exclusion Criteria 7.2.4.1 Rationale for Continued Treatment 7.2.4.2 Discontinuation of Study Treatment 8 Study Treatment 8.6 Accountability	Added Cohort 2 for the combination of glembatumumab vedotin and varlilumab based on the rationale that combining cytotoxic therapy with immunotherapy can result in synergistic activity; this new cohort resulted in the following changes: • Study title • Included varlilumab as investigational treatment • Increased the number of patients in study overall • Included combination treatment in study objectives • Immune-mediated RECIST (irRECIST) as supplementary, retrospective assessment • Added treatment-limiting toxicity rules and dose modifications • Revised eligibility criteria: o Inclusion #5, submission of visceral tumor lesions for patients with non-cutaneous disease; new requirement of skin fold biopsy for biomarker analysis o deletion of exclusion #10, *"Systemic radiation therapy within 4 weeks, prior focal radiotherapy within 2 weeks, or radiopharmaceuticals (strontium, samarium) within 8 weeks prior to the first dose of study treatment"* and revision of inclusion #5 to encompass the safety intent, *"Resolution of toxicities related to prior therapies* ***(including radiotherapy)*** *to ≤ NCI-CTCAE Grade 1 severity, except for alopecia, grade 2 fatigue, vitiligo, or endocrinopathies on replacement therapy".* • Additional exclusion criteria for safety measures: 18. "*Previous treatment with varlilumab or other anti-CD27 mAb*" 19. "*Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment*" 20. "*Use of immunosuppressive medications within 4 weeks or systemic corticosteroids within 2 weeks prior to first dose of study treatment. Topical, inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Non-absorbed*

	intraarticular corticosteroid and replacement steroids (<10 mg/day prednisone or equivalent) will be permitted" 21. "*Active autoimmune disease or a documented history of autoimmune disease, or history of potential autoimmune syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo, endocrinopathies, type 1 diabetes, or patients with resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger (e.g., drug-related serum sickness or post-streptococcal glomerulonephritis). Subjects with mild asthma who require intermittent use of bronchodilators (such as albuterol) who have not been hospitalized for asthma in the preceding 3 years will not be excluded from the study.*" • Criteria for safety evaluation for immunotherapy • Statistical methods • Section 5.3 Varlilumab: nonclinical and clinical summaries; rationale for study design, dose, and continued treatment • Section 8.2 Varlilumab: new section on description of drug product; storage; preparation and administration • Section 8.3.2: new section on dose modifications • Section 8.4: new section on treatment-limiting toxicity definition and rules • Sections 8.5.2 and 8.5.3: new sections on previously observed and management of toxicities added for investigator guidance
3 Synopsis 4 Schedule of Assessments Footnote 5 5.4.2.1 Rationale for Permitting Continued Treatment in Cases of Suspected Progressive Disease 7.1 Overall Design and Plan of the Study 7.2.4.1.1 Allowance for Permitting Continued Treatment in Cases of Suspected Progressive Disease	Allowed for continued treatment administration in Cohort 2 for apparent disease progression due to potential inflammatory responses and/or kinetics of immunotherapy response
2 Glossary of Abbreviations 15 References	Included terms and references relevant to varlilumab and immunotherapy
4 Schedule of Assessments	With addition of Cohort 2: • Table 1, Footnote 15: For consistency with exclusion criterion 19, added the requirements of microscopic examination of urinalysis at baseline and negative urine culture prior to enrollment if infection is suspected; included thyroid function tests • Table 1, Footnote 25: added hematology, chemistry, and adverse event monitoring on Cycle 1 Days 7 and 14 for safety measures; to minimize patient burden footnote 25 states that AE monitoring could be performed in person or by telephone call • Table 1, Footnotes 18, 19: added PBMC and PK collection at cycles 1, 2, and 5 as this dosing regimen has not been investigated; also deleted PMBC collection at EOT for Cohort 1 • Table 1, Footnotes 3, 22: specified treatment visits and varlilumab administration • Footnote 21: provided details on sequence of infusions for clarity

	For biomarker analyses: • Table 1, Footnote2 7, 8: for consistency with revised inclusion criterion 5, added the requirement of skin fold biopsy obtained within 12 weeks of study entry • Footnote 9: added language to encourage submission of tumor tissue at recurrence
8.1.3 Preparation and Administration 8.5 Potential Toxicity and Management of Toxicity	Added guidelines for the prevention, monitoring, and management of infusion site extravasation for safety Revised Section 8.5 (formerly Section 8.1.7) to include and management of most common and severe toxicities; referral to Investigator's Brochure which is updated on an annual basis
9 Concomitant Therapy	Provided guidance consistent with language in other varlilumab protocols
10.2.1.1 Anti-Tumor Activity 11.1 Analysis Endpoints	Included irRECIST criteria as additional analysis as varlilumab is an immunotherapy
10.2.1.4 Pharmacodynamics	Provided further detail that immune response assessments may be performed due to addition of immunotherapy to protocol
10.2.2.3 AE/SAE reporting 10.2.2.4 Rapid Notification of AE of Interest 10.2.2.6 Other Safety Data	Further defined reporting period after varlilumab treatment Added new Section 10.2.2.4 and language on AE monitoring and reporting for safety considerations Deleted now redundant text in Section 10.2.2.2
Synopsis, Statistical Methods 11. Statistical Considerations	Included analyses and methods for Cohort 2, number of patients, and irRECIST criteria
Throughout	Formatting modifications and typographical corrections; added varlilumab as appropriate when study treatment was referenced

The following changes have been made to Protocol CDX011-05 as Amendment 1:

SECTION(S)	CHANGE/RATIONALE
Protocol Synopsis, Number of Study Centers	Increased number of participating centers from 'up to 10' to 'approximately 15'; additional centers are being pursued to enhance enrollment.
Protocol Synopsis, Eligibility Criteria Section 7.2.2. Subject Eligibility	Inclusion Criteria #3: Changed the timing of documented progressive disease from 'at study entry' to 'during or subsequent to the last anticancer therapy' for clarification. Inclusion Criteria #4: -Deleted limit of no more than four prior anticancer regimens to reflect changing standard of care and to facilitate enrollment. -Deleted "locally advanced/recurrent/metastatic" which are examples of advanced disease settings but are not intended to be strict criteria. -Deleted prior ipilimumab requirement and inserted "at least one prior check-point inhibitor (e.g., anti-CTLA-4, PD-1, PD-L1 targeted immunotherapy)" to reflect changing standard of care/revised NCCN guidelines, and to facilitate enrollment. Inclusion Criteria #5: Changed 'confirmation' of gpNMB expression to 'evaluation' for clarity. Exclusion Criteria #4: Corrected typographical error

	by changing the wash-out period for the use of chemotherapy to be 'within 2 weeks or 5 half-lives (whichever is longer)' from '(whichever is shorter)'
Protocol Synopsis, Criteria for Evaluation	Added ECOG assessment to Safety evaluations for consistency with ECOG assessment in Section 10.2.2.5 Added "such as gpNMB-expressing myeloid-derived suppressor cells" as an example of immune response cells of interest.
Protocol Synopsis, Statistical Methods 11. Statistical Considerations (and all sub-sections)	Added "ECG parameters" and "ECOG performance status" to safety analysis endpoints for consistency with Protocol Synopsis and Section 10.2.2.5. Clarified that the evaluable population will be used for the primary analysis of ORR, but that additional efficacy analyses will be based on the ITT (treated) population. Deleted the Atkinson & Brown reference as the statistical methodology in this reference is not relevant. Changed significance level from 1% to 5% to reflect one-stage study design: A one-sample exact binomial test with one-sided significance level of 5% will be used to test the response rate under the null and alternative hypotheses.
4. Schedule of Assessments Table 1 Footnote 18	Deleted time point for PD sample collection at cycles 3, 4, 5, etc. to reduce study burden while still allowing for adequate PD assessment through cycle 2 and end of treatment. Clarified time points accordingly in footnote.
5.1 Advanced Melanoma, Table 2 Appendix 6	E Expanded this section to update with FDA-approval of nivolumab and pembrolizumab in 2014 and included results of the pivotal trials; updated relevant tables.
5.3 Glembatumumab Vedotin Table 4, Figure 1	Updated Table 4 and Figure 1 with final results from the CDX011-03 "EMERGE" study according to ITT methodology, which includes all enrolled patients, but does not include cross-over phase data.
5.5 Study Rationale	Added nivolumab and pembrolizumab to the list of check-point inhibitors that patients enrolled in this trial have previously received for consistency with revised inclusion criteria.
Throughout	Formatting adjustments and typographical corrections