SUMMARY OF CHANGES – PROTOCOL

For Protocol Amendment # to: A Phase 2 Study of CDX-011 (glembatumumab vedotin) for Metastatic Uveal Melanoma

NCI Protocol #: 9855
Local Protocol #: NCI9855

NCI Version Date: April 2, 2018
Protocol Date: April 2, 2018

#	Section	Change
1.	**TITLE PAGE**	Updated protocol and number date
2.	3.1.4 **(p. 12)**	Updated CTCAE v4 to v5 All prior treatment-related toxicities must be CTCAE v5 grade ≤ 1 (except alopecia). Certain exceptions apply, such as immunotherapy-induced hypothyroidism or adrenal insufficiency or panhypopituarism requiring stable doses of hormone replacement or rash from prior therapy.
3.	**5.1(p.20)**	Updated CTCAE v4 to v5 Patients with Grade 3 or 4 infusion related reactions as defined by CTCAE v.5.0 may be re-challenged with treatment on a case-by-case basis after discussion with Lead PI, CTEP drug monitor, and any others deemed necessary. These cases will be tracked and monitored carefully.
4	6 **(p.23)**	Updated CTCAE v4 to v5 Patients with Grade 3 or 4 infusion related reactions as defined by CTCAE v.5.0 may be re-challenged with treatment on a case-by-case basis after discussion with Lead PI, CTEP drug monitor, and any others deemed necessary. These cases will be tracked and monitored carefully.

#	Section	Change
5	7.2 **(p.27)**	Updated CTCAE version 4.0 to version 5.0 **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
6	**7.3 (p.28)**	Updated the language to reflect NCI request sent on 1/25/2018 regarding the new term for Progressive Disease. Expedited Reporting Guidelines Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports. **Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.** Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted. Rationale: Under 7.3 Expedited Reporting Guidelines, the language needs to change to reflect the amendment request from NCI's letter (attached) on 1/25/2018 regarding new term for Progressive Disease.

TITLE PAGE

NCI Protocol #: 9855

Local Protocol #: *NCI9855*

ClinicalTrials.gov Identifier: NCT02363283

TITLE: A Phase 2 Study of CDX-011 (glembatumumab vedotin) for Metastatic Uveal Melanoma

Corresponding Organization: LAO-TX035 / University of Texas MD Anderson Cancer Center LAO

Principal Investigator: Sapna P. Patel, MD
MD Anderson Cancer Center
Melanoma Medical Oncology
Houston, TX 77030
Phone: 713-792-2921
Fax: 713-745-1046
E-mail: sppatel@mdanderson.org

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

Statistician:
Roland Bassett
MD Anderson Cancer Center
1515 Holcombe Blvd Houston, TX 77030
Tel: 713-563-4272
rlbasset@mdanderson.org

Study Coordinator:
Manolo Pasia Jr.
Clinical Research Support Center
MD Anderson Cancer Center
1515 Holcombe BlvdUnit 1635
Houston, TX 77030
Tel: 713-563-7247
Fax: 713-563-5468
ClinicalResearchSupport@mdanderson.org

Responsible Research Nurse:
Karen Perdon
MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 0430
Houston, TX 77030
Tel: 713-794-4117
Fax: 713-745-1046
kbperdon@mdanderson.org

Responsible Data Manager:
Edwina Washington
MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 0430
Houston, TX 77030
Tel: 713-792-2921
Fax: 713-745-1046
ewwashin@mdanderson.org

NCI Supplied Agents: CDX-011 (glembatumumab vedotin) (NSC 763737)

IND #: 126619

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original / Version Date: January 7, 2015
Revision #1/Version Date: March 25, 2015
Revision #2/Version Date: April 21, 2015
Revision #3/Version Date: June 29, 2015
Revision #4/Version Date: July 27, 2015
Amendment #1/Version Date: February 29, 2016
Amendment #2/Version Date: August 2, 2016
Amendment #3/Version Date: September 2, 2016
Amendment #4/Version Date: March 23, 2017
Amendment # 5 / Version Date: April 2, 2018

SCHEMA

This trial is a single-arm, open-label Phase II study of CDX-011 (glembatumumab vedotin) in patients with metastatic uveal melanoma. The primary endpoint is overall response rate (ORR) using RECIST 1.1. Secondary endpoints include GPNMB expression, progression-free survival (PFS), overall survival (OS), as well as toxicity analysis. Exploratory endpoints include characterizing the anti-tumor immunophenotype of patients receiving CDX-011 (glembatumumab vedotin) as well as post-hoc correlation of rash with PFS and ORR.

All treatment will be performed in the outpatient setting. Up to 34 patients will be treated with CDX-011 (glembatumumab vedotin).

The study schema is as follows:

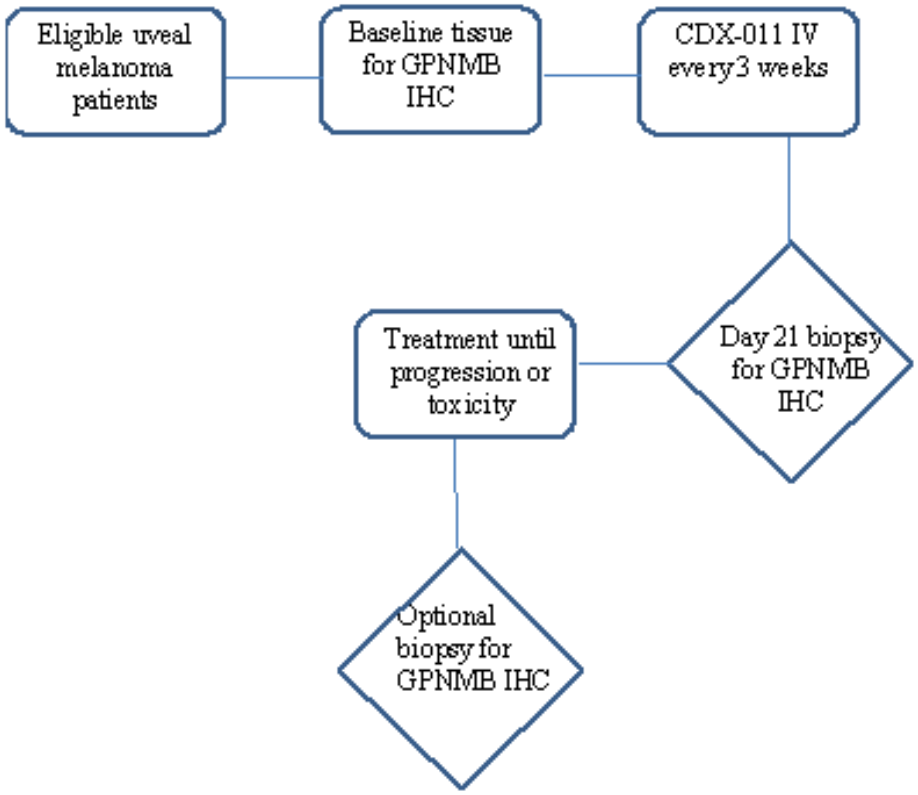


TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

The primary objective of this study is to characterize the clinical anti-tumor activity of CDX-011 (glembatumumab vedotin) as a single-agent in the treatment of patients with metastatic uveal melanoma. The primary endpoint will be overall response rate (ORR) using RECIST 1.1.

1.2 Secondary Objectives

Secondary objectives include a description of the clinical safety and benefit of CDX-011 (glembatumumab vedotin) and pharmacodynamics changes in glycoprotein NMB (GPNMB) expression. Secondary endpoints will include progression-free survival (PFS), overall survival (OS), GPNMB expression via immunohistochemistry (IHC).

1.3 Exploratory Objectives

Exploratory objectives for this study include characterization of the anti-tumor immunophenotype of patients receiving treatment. Post hoc, correlation of rash with clinical benefit, or lack of rash with lack of benefit, will also be explored.

2. BACKGROUND

2.1. Eye Neoplasm, Uveal Melanoma

Uveal melanoma accounts for 5% of all melanoma diagnoses, representing approximately 2,000 patients per year in the U.S.[1] The uveal tract of the eye is not drained by lymphatics and 50% of uveal melanoma patients will develop metastasis via hematogenous spread, the overwhelming majority of which (90%) occur in the liver.[2-5] Once metastatic, average survival is 6 months. Outside of prostate cancer metastasizing to bone, there is no other solid tumor which demonstrates such a predictable homing for its metastatic site.

To date there is no standard of care approved treatment option for patients with metastatic uveal melanoma and expert consensus guidelines recommend treatment on a clinical trial. Surgical resection of liver metastasis plays a role in less than 10% of patients, in part due to the need for liver-only disease and less than 50% liver involvement, and the advanced age of metastatic uveal melanoma patients (50-60 years old).[6]

A few approaches to systemic therapy have been studied or are newly underway. Chemotherapy alone has generated response rates of less than 1% for metastatic uveal melanoma.[7-8] Biochemotherapy consisting of bleomycin, vincristine, lomustine, dacarbazine, and interferon-alpha (BOLD-IFN) resulted in a response rate of 20% but its use is marred by significant hematologic and unpredictable pulmonary toxicity.[9]

Targeted therapy with IMC-A12 (Cixutuxumab), an IGF-1R blocking antibody, has been studied

in a Phase II trial in metastatic uveal melanoma (CTEP 8832) with zero responses seen in 18 patients enrolled (unpublished data). AZD-6244 (Selumetinib), a selective MEK inhibitor, was studied in a randomized Phase II trial versus temozolomide in patients with metastatic uveal melanoma. Selumetinib demonstrated a final overall response rate of 10% versus 0% in the temozolomide arm.[10] No significant difference in overall survival was noted. Imatinib and sunitinib trials targeting CKIT overexpression in uveal melanoma have likewise been unsuccessful with response rates of 0% and 5% in published clinical trials.[11, 12]

There are several other studies in progress using various agents such as targeted therapy, epigenetic therapy, and immunotherapy. Trametinib, a selective MEK inhibitor, with or without GSK2141795 (Akt inhibitor) is being studied in a randomized Phase II trial (NCI 9445, NCT01979523). Currently more than 1/3 of the study population has been enrolled (N=80) with no interim results reported. AEB071 (PKC inhibitor, Sotrastaurin) is being studied as both monotherapy in a Phase I study for metastatic uveal melanoma (NCT01430416) as well as in combination with a MEK inhibitor, MEK162 (Binimetinib) in a separate Phase I/II study (NCT01801358) for this patient population. Ipilimumab is being studied in a dedicated Phase I/II study solely for uveal melanoma patients at two dose levels: 3 mg/kg and 10 mg/kg (NCT01585194). To date, results have not been reported. Vorinostat as an epigenetic modifier is under investigation in a Phase II study to assess efficacy for metastatic uveal melanoma (NCT01587352). No results have been reported for vorinostat.

2.2. CTEP IND Agent – CDX-011 (glembatumumab vedotin)

Glycoprotein NMB (GPNMB) is a transmembrane protein whose overexpression promotes invasion and metastasis of cancer cells from multiple tissue types and is expressed at high levels in several malignant human tissues, including uveal melanoma, relative to corresponding normal tissue.[13,14] Preliminary data consisting of immunohistochemistry (IHC) of 21 uveal melanoma specimens demonstrated staining in 86% of samples tested.[15] The percentage of cells positive per tumor ranged from 10-90% and the level of GPNMB was of variable intensity (5 tumors 1+; 11 tumors 2+; and 2 tumors 3+).

Antibody-drug conjugates offer a novel approach to treating cancer and allow for the selective delivery of cytotoxic agents to a tumor with the goal of reducing toxicity and enhancing efficacy compared with the systemic administration of cytotoxic agents or unconjugated antibodies. CDX-011 (glembatumumab vedotin) is a fully-human IgG2 monoclonal antibody (CR011) directed against GPNMB coupled via a protease-sensitive valine-citrulline peptide linker to monomethylauristatin E (MMAE), a potent cytotoxic microtubule inhibitor.[16] This technology is licensed from Seattle Genetics and is identical to that used in SGN35, a promising antibody-drug conjugate for lymphoma. The proposed mechanism of action is that, upon binding to GPNMB on tumors, the complex is internalized and MMAE is released via proteolytic cleavage of the valine-citrulline linker inside a lysosome. Tumor cell death occurs as a result of microtubule inhibition by MMAE leading to cell-cycle arrest. Bystander tumor cells may be also be killed by uptake of free MMAE released by dying cells. CDX-011 (glembatumumab vedotin) induced complete regression of GPNMB-expressing tumors derived from SK-Mel-2 and SK-Mel-5 melanoma cell lines in xenograft mouse studies.[13,14,17]

Pharmacology

CDX-011 (glembatumumab vedotin) binds to and inhibits growth of GPNMB-positive tumor cell lines including the melanoma lines SK-Mel-2 and SK-Mel-5 (IC50 216-300 ng/mL).[13] It has no effect on GPNMB-negative cell lines. CDX-011 (glembatumumab vedotin) also induces cell-cycle arrest followed by apoptotic cell death in GPNMB-expressing melanoma cells. In SK-Mel-2 and SK-Mel-5 melanoma xenograft mouse models, CDX-011 (glembatumumab vedotin) administered intravenously (IV) once daily every 4 days x 4 led to durable tumor regression in a dose-dependent manner.[17]

Pharmacokinetics

The pharmacokinetics (PK) of total CR011 antibody (conjugated and free) have been assessed in rodents and primates. The data demonstrate dose-proportional exposure and elimination half-life of 11-22 hours in cynomolgus monkeys, increasing with dose. Concentration vs. time plots appeared non-linear with dose, suggestive of saturable elimination pathways. Overall, there was no significant antibody accumulation after 4 weekly doses, and levels of free MMAE were low compared to levels of total antibody, supporting the premise that the CR011-MMAE bond was stable in extracellular matrix.

PK data for serum concentrations of CDX-011 (glembatumumab vedotin) were collected for 55 melanoma patients. First-order kinetics were observed following a 90-minute IV infusion. The half-life (t ½) was approximately 27 hours at 1.88 mg/kg.

Mechanism of Action

The proposed mechanism of action of CDX-011 (glembatumumab vedotin) is via binding of the antibody-drug conjugate to GPNMB on tumor cells. The antibody-GPNMB complex is then internalized and cytotoxic MMAE is released via cleavage of the valine-citrulline peptide linker inside a lysosome. MMAE leads to microtubule inhibition causing cell cycle arrest.

Route of Elimination

CDX-011 (glembatumumab vedotin) is cleared by the liver and excreted via the kidneys.

Toxicology

In cynomolgus monkeys, the no observable adverse effect level (NOAEL) for CDX-011 (glembatumumab vedotin) administered once weekly for 4 weeks was 0.3 mg/kg in males and 1 mg/kg in females. The major toxicity was in the hematopoietic system. All findings, including microscopic effect were completely reversible. Neutropenia was considered a dose-limiting toxicity and was reversible following a 6-week recovery period. The maximum-tolerated dose (MTD) in both sexes was considered to be between 1 mg/kg and 3 mg/kg.

In repeat-dose rat studies, dose-dependent findings were observed for CDX-011 (glembatumumab vedotin) treated groups with similar hematopoietic findings in rats treated with the highest dose of CDX-011 (glembatumumab vedotin) as in rats treated with MMAE alone. All findings were reversible except for dose-dependent germ cell depletion in the testes of male animals. No findings were attributed to CR011 antibody alone or vehicle control.

Clinical activity of CDX-011 (glembatumumab vedotin)

To date, CDX-011 (glembatumumab vedotin) has been administered to more than 255 cancer patients in three completed clinical trials. CDX-011 (glembatumumab vedotin) has demonstrated clinical activity with an acceptable safety profile in a Phase I/II dose escalation and expansion study in advanced melanoma (n=117).[18] A dose level of 1.88 mg/kg administered intravenously every 3 weeks was determined to be the maximum tolerated dose (MTD). At the MTD, the most common treatment-related toxicities included dermatologic events (rash, pruritus, alopecia), fatigue, neutropenia, neuropathy, and gastrointestinal toxicities (diarrhea, nausea, dysgeusia, constipation, and vomiting). In this study, the ORR was 13% in 40 patients at the 1.88 mg/kg dose level, including one response that was not confirmed. The disease control rate (DCR = PR + SD ≥ 12 months) was 81%. PFS at the MTD was 3.3 months.

In the melanoma study, treatment-related adverse events that occurred in >20% of patients at the MTD, also known as the Phase II dose, were fatigue, rash, nausea, neuropathy, alopecia, pruritus, constipation, diarrhea, anorexia, and dysgeusia. Grade 3 or greater treatment-related events consisted primarily of neutropenia, neuropathy, fatigue, and rash. Three fatal events considered potentially related to CDX-011 (glembatumumab vedotin) treatment occurred in the melanoma study: pneumococcal sepsis, acute renal failure and toxic epidermal necrolysis.

Results from the CDX-011 (glembatumumab vedotin) studies completed to date have revealed the following:

- CDX-011 (glembatumumab vedotin) is active in both breast cancer and melanoma. Activity data (objective response rates and progression-free survival) for patients treated at the Phase II dose across all studies have been favorable for the heavily-pretreated populations studied.
- Alternate dosing schedules (every 1 week, every 2 weeks, and every 3 weeks) were evaluated in the melanoma study. Although indications of increased activity were noted in the more frequent dosing cohorts, this was associated with increased toxicity.
- Although sample sizes are small, patients with tumors expressing higher levels of GPNMB consistently appear to derive greater clinical benefit from CDX-011 (glembatumumab vedotin) as compared the entire population of treated patients.
- In both breast cancer studies, the subset of patients with triple-negative breast cancer, where treatment options are limited, also appeared to derive greater clinical benefit from CDX-011 (glembatumumab vedotin).
- In the melanoma study, development of rash of any grade, which may be related to the presence of GPNMB in the skin, within the first 21 days of treatment was associated with greater progression-free survival (PFS) and objective response rate.[18] Rash also

correlated with prolonged PFS in the Phase II breast cancer study (EMERGE), although this correlation was not observed in the earlier Phase I/II breast cancer study (CR011-CLN-20).[19]

2.3. Rationale for Proposed Study

GPNMB is a transmembrane protein whose overexpression promotes invasion and metastasis of cancer cells from multiple tissue types and is expressed at high levels in several malignant human tissues, including uveal melanoma, relative to corresponding normal tissue.[13,14] GPNMB is associated with induction of matrix metalloproteinase-3, which may provide a mechanism by which this protein promotes tumor invasion. In previous work from MD Anderson Cancer Center, IHC analysis of 21 uveal melanoma specimens demonstrated staining in 86% of samples tested.[15] The percentage of cells positive per tumor ranged from 10-90% and the level of GPNMB was of variable intensity (5 tumors 1+; 11 tumors 2+; and 2 tumors 3+).

Because of this high-frequency expression on uveal melanoma cells, targeting GPNMB with CDX-011 (glembatumumab vedotin) represents a possible therapeutic avenue. In previous clinical experience using CDX-011 (glembatumumab vedotin) in cutaneous melanoma patients, overall response rate of 13% was seen in patients treated at the MTD, also known as the Phase II dose. Clinical experience with CDX-011 (glembatumumab vedotin) in uveal melanoma patients is not yet known and an effective therapy for metastatic uveal melanoma patients is a current unmet need.

Patients with metastatic uveal melanoma will be eligible regardless of upfront GPNMB status. This is due to the high frequency of GPNMB expression in uveal melanoma samples (86%) noted previously.[15] To clarify pharmacodynamics of CDX-011 (glembatumumab vedotin), baseline samples as well as Day 21 on-treatment tumor tissue samples will be analyzed retrospectively for GPNMB expression.

2.4. Exploratory/Correlative Studies Background

Immunophenotype of patients

Because GPNMB inhibition with CDX-011 (glembatumumab vedotin) may alter the tumor microenvironment, we plan as an exploratory endpoint to analyze immune and inflammatory cell infiltrates in tumor samples. These findings will help coordinate future efforts of combining CDX-011 (glembatumumab) with either immunotherapy such as checkpoint blockade or with anti-inflammatory agents such as iNOS inhibitors or triterpenoid anti-inflammatory agents. The timing of combination therapy may be elucidated if infiltrates change in response to treatment.

The immune effects of targeted therapy in cutaneous melanoma has been described *in* vitro as well as in patients receiving BRAF-targeted therapy.[20] Treatment with either BRAF inhibitor alone or in combination with MEK inhibitor is associated with an increased expression of melanoma antigens MART-1 and gp100 and an increase in CD8+ T-cell infiltrate. Similarly,

immunosuppressive cytokines interleukin-6 and interleuin-8 are decreased with treatment while tumor programmed death ligand-1 (PDL1) increased with treatment.
These same markers of immune effects can be measured in uveal melanoma patients receiving targeted therapy with CDX-011 (glembatumumab vedotin). IHC for melanoma antigens and enumeration of T-cell infiltrate is planned at baseline and after 21 days on treatment. Additionally, evaluation for NK cells, Foxp3+ regulatory T lymphocytes, macrophages (CD68+), as well as markers of mature activated dendritic cells (CD40+/CD83+) is planned. It is hypothesized that treatment with CDX-011 (glembatumumab vedotin) will increase cytotoxic CD8+ T-cell infiltrate while decreasing immunosuppressive cytokines. If true, this can form the rational basis for timed combination therapy with checkpoint blockade, as was similarly elucidated in cutaneous melanoma patients receiving BRAF-targeted therapy.[21]

Correlate rash with response

In the melanoma study CR011-CLN-11, development of rash, which may be related to the presence of GPNMB in the skin, was associated with greater PFS and ORR.[18] Rash also correlated with prolonged PFS in the Phase II breast cancer study (EMERGE), although this correlation was not observed in the earlier Phase I/II breast cancer study (CR011-CLN-20).[19]

For this study, patients with uveal melanoma will be assessed for development of rash and this will be correlated with ORR and PFS.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Patients must have histologically or cytologically confirmed metastatic or locally recurrent uveal melanoma. Because histologic or cytologic confirmation of primary uveal melanoma is not always possible the confirmation of the clinical diagnosis of uveal melanoma by the treating investigator is allowed. Clinical diagnosis of uveal melanoma is often made by an ophthalmologist, not by tissue diagnosis. If an ophthalmologist diagnosed and treated a patient for uveal melanoma in the past, it is sufficient for a clinical diagnosis.

3.1.2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3. The study will be limited to patients who are chemotherapy-naïve. Patients may have received prior systemic or liver-directed local therapies for advanced uveal melanoma as long as those treatments do not involve chemotherapy. This includes, but is not limited to:, immunotherapy, targeted therapy, , transarterial embolization, radiofrequency ablation, or cryoablation. Treatment must be completed at least 28 days prior to initiation of study therapy. Radiation therapy is also allowed and must be completed at least 28 days prior to initiation of study therapy. Lesions treated via radiation or liver-directed therapy may not be used as target lesions unless they demonstrate growth over a minimum of 3 months on subsequent imaging.

3.1.4. All prior treatment-related toxicities must be CTCAE V5 grade ≤ 1 (except alopecia). Certain exceptions apply, such as immunotherapy-induced hypothyroidism or adrenal insufficiency or panhypopituarism requiring stable doses of hormone replacement or rash from prior therapy.

3.1.5. Age ≥18 years. Because no dosing or adverse event data are currently available on the use of CDX-011 (glembatumumab vedotin) in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.6. ECOG performance status ≤2

3.1.7. Life expectancy of greater than 3 months.

3.1.8. Patients must have normal organ and marrow function as defined below:

- leukocytes ≥3,000/μL
- absolute neutrophil count ≥1,500/ μL
- platelets ≥100,000/ μL
- total bilirubin ≤ 1.5 x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal; ≤5 x institutional upper limit of normal if liver metastasis present
- Creatinine ≤ institutional upper limit of normal

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.9. The effects of CDX-011 (glembatumumab vedotin) on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control;

abstinence) prior to study entry, for the duration of study participation, and for 4 months after last CDX-011 (glembatumumab vedotin) dose. Women of child-bearing potential must have a negative serum pregnancy test within 14 days prior to start of protocol treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of CDX-011 (glembatumumab vedotin) administration.

3.1.10. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Patients with a history of another malignancy except for those who have been disease-free for 2 years. Patients with a history of definitively treated non-melanoma skin cancer or squamous cell carcinoma of the cervix are eligible. Patients with definitively treated in-situ cancers are eligible, regardless of timeframe.

3.2.2. Patients with neuropathy > grade 1.

3.2.3. Patients who are receiving any other investigational agents. If the patient received a previous investigational or other agent or treatment, a washout period of 4 weeks is required.

3.2.4. Patients receiving any medications or substances that are substrates of CYP3A4will be closely monitored for toxicity. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6. HIV-positive patients on antiretroviral medications that are CYP3A4 substrates will be closely monitored. HIV-positive patients will be excluded if they have a CD4 count <200 as these patients have an increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.7. Pregnant or nursing women.

3.2.8. Patients who have previously received CDX-011 (glembatumumab vedotin) or other MMAE-containing agents.

3.2.9. Patients with a history of allergic reactions attributed to compounds of similar composition to dolastatin or auristatin (e.g. Auristatin PHE, Auristatin PE, and symplostatin).

3.3. Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to

the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1. Investigator and Research Associate Registration with CTEP

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP

Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.2. Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to the CTSU Regulatory Office before they can be approved to enroll patients.

The CTSU Regulatory Office tracks receipt of these documents in the CTSU Regulatory Support System (RSS), reviews for compliance, and transmits site approval data to CTEP.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing, or amendment review However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (*i.e.*, laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9855 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the Lead Organization folder to expand, then select LAO-TX035, and protocol

#9855.

- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will automatically load to RSS.)

4.2.2 Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval *(and if applicable,* Model Informed Consent) to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.2.3 Checking Site Registration Status

Sites can check the status of their registration packets by querying the Site Registration subtab of the members' section of the CTSU Web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
Click on the Regulatory tab at the top of your screen.
Click on the Site Registration subtab.
Enter your 5-character CTEP Institution Code and click on Go.

Note: If possible, please allow three working days for site registration approval before attempting to enroll your first patient.

4.3. Patient Registration Procedures

OPEN/ IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN will automatically transfer to the NCI's clinical data management system, Medidata Rave.

NCI 9855 will use the IWRS slot reservation system. For trials with slot reservation

requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment. Please refer to the section below for additional instructions on how to use the IWRS slot reservation system.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

OPEN/IWRS User Requirements

OPEN users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form.

<u>Patient Enrollment Instructions</u>

- Sites must reserve a slot in IWRS. Each site is allowed 2 slot reservations at a time with a 2 day guaranteed hold for each slot.

- Next, fax the following documents for review:
  1. Latest clinic note
  2. Pathology report
  3. Radiology report

- Fax to: K. Perdon/S. Patel, MD at (713) 794-1493. Include your contact information in the fax cover sheet.

- Each reservation will need to be authorized and approved by an MD Anderson designee prior to registering the patient in OPEN. Once the slot is approved in IWRS, you may proceed with registering your patient in OPEN.

Following registration, patients should begin protocol treatment within 7 days. Issues

that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website:

http://www.theradex.com/downloads/IWRS%20User%20Guide.pdf)

This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com

CORe registration at MD Anderson sites only

In addition to OPEN registration, patients will also be registered in Clinical Oncology Research System (CORe, www.oncologyresearch.org)

To register a patient, the research nurse will:

- Confirm patient eligibility
- Obtain informed consent, electronic or paper version
- Confirm insurance approval of clinical trial treatment

To complete the registration process, the research nurse will:

- Register the patient in CORe
- Assign a patient study number
- Assign the patient a treatment start date

5. TREATMENT PLAN

5.1. CDX-011 (glembatumumab vedotin) Administration

Treatment will be administered on an outpatient basis at a starting dose of CDX-011 (glembatumumab vedotin) of 1.9 mg/kg IV every 3 weeks. Reported adverse events and

potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

- CDX-011 (glembatumumab vedotin) solution is diluted with 5% dextrose injection before infusion. CDX-011 (glembatumumab vedotin) is administered as a 90-minute(+/- 10 minutes) IV infusion using a 0.22 µm in-line filter at a dose of 1.9 mg/kg IV every 3 weeks (+/- 3 days)

- There are no premedications recommended for CDX-011 (glembatumumab vedotin) on the first dose. Subjects should be carefully monitored for infusion reactions during CDX-011 (glembatumumab vedotin) administration. If an acute infusion reaction is noted, subjects should be managed according to Appendix C. After symptoms have resolved, the infusion may be resumed at half the initial rate, or as otherwise directed by the attending physician/PI.

- If an infusion reaction occurs, vital signs should be monitored every 5 minutes during infusion until stable. After infusion is complete, vital signs should be monitored per institutional infusion standard.

- Patients with Grade 3 or 4 infusion related reactions as defined by CTCAE v.5.0 may be re-challenged with treatment on a case-by-case basis after discussion with Lead PI, CTEP drug monitor, and any others deemed necessary. These cases will be tracked and monitored carefully.

- Actual body weight will be recorded and used to calculate dose prior to each infusion.

5.2. General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of CDX-011 (glembatumumab vedotin) with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes, specifically CYP3A4. Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.3. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4. Duration of Follow Up

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients removed prior to progression of disease will be followed for PFS and OS per intent-to-treat analysis.

5.5. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

CDX-011 (glembatumumab vedotin) should be administered at a dose of 1.9 mg/kg IV every 3 weeks. Dosing delays are allowed up to 3 weeks. A delay longer than 3 weeks warrants removal from study.

Dose Level	CDX-011 (glembatumumab vedotin) Dose
0	1.9 mg/kg every 3 weeks
-1	1.3 mg/kg every 3 weeks
-2	1 mg/kg every 3 weeks

Dose reduction levels are outlined in the table above. Criteria for dose modifications include nausea, diarrhea, and neutropenia and are outlined in the tables below. If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Diarrhea	Management/Next Dose for CDX-011 (glembatumumab vedotin)
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	Management/Next Dose for CDX-011 (glembatumumab vedotin)
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Growth factor support	

Rash	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 1-2	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: topical or systemic corticosteroids	

Neuropathy	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 1	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: anaglesia	

Fatigue	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 1-2	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**

Fatigue	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Growth factor support	

Non-Hematologic Toxicity	Management/Next Dose for CDX-011 (glembatumumab vedotin)
Grade 3-4	Hold* until ≤ Grade 2. Resume at one dose level lower, if not resolved to ≤ Grade 2 after 72 hours.** Supportive measures as clinically indicated.
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

- If an infusion reaction occurs, vital signs should be monitored every 5 minutes during infusion until stable. After infusion is complete, vital signs should be monitored per institutional infusion standard.

- Patients with Grade 3 or 4 infusion related reactions as defined by CTCAE v.5.0 may be re-challenged with treatment on a case-by-case basis after discussion with Lead PI, CTEP drug monitor, and any others deemed necessary. These cases will be tracked and monitored carefully.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1. Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs) for CDX-011 (glembatumumab vedotin) (CDX-011, NSC 763737)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the

Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.
Frequency is provided based on 255 patients. Below is the CAEPR for CDX-011 (glembatumumab vedotin) (CDX-011).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1 August 3, 2016[1]

Adverse Events with Possible Relationship to CDX-011 (glembatumumab vedotin) (CTCAE 4.0 Term) [n= 255]			**Specific Protocol Exceptions to Expedited**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Infusion site extravasation	
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		
	White blood cell decreased		

Adverse Events with Possible Relationship to CDX-011 (glembatumumab vedotin) (CTCAE 4.0 Term) [n= 255]			**Specific Protocol Exceptions to Expedited**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Myalgia		
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
	Nervous system disorders - Other (peripheral neuropathy)[3]		***Nervous system disorders- Other (peripheral neuropathy)[3] (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		
	Pharyngolaryngeal pain		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary embolism)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		
	Hyperhidrosis		
	Palmar-plantar erythrodysesthesia syndrome		
Pruritus			***Pruritus (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (nail disorder)[4]		
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Peripheral neuropathy includes Peripheral motor neuropathy and Peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

[4]Rash includes exfloliative rash, Erythema, Rash erythematous, Rash generalized, Rash macular,

Rash papular, Rash maculo- papular, Catheter site rash and Infusion site erythema under SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

[5]Nail disorder includes nail loss, onychoclasis and dermatomyositis under SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

Adverse events also reported on CDX-011 (glembatumumab vedotin) (CDX-011) trials but with the relationship to CDX-011 (glembatumumab vedotin) (CDX-011) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia, bone marrow failure); Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Palpitations; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (hypoacusis); Ear pain
Endocrine disorders - Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Conjunctivitis; Dry eye; Eye disorders - Other (ocular hyperemia); Photophobia; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dysphagia; Fecal incontinence; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (hyperchlorhydria); Gastrointestinal disorders - Other (tongue ulceration); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Oral dysesthesia; Oral pain; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (axillary pain); Injection site reaction; Irritability; Localized edema; Malaise; Non-cardiac chest pain
Hepatobiliary disorders - Hepatic pain
Immune system disorders - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (excoriation); Wound complication
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Creatinine increased; GGT increased; Lymphocyte count decreased; Urine output decreased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (restless legs syndrome); Musculoskeletal and connective tissue disorder - Other (shoulder pain); Musculoskeletal and connective tissue disorder - Other (trigger finger); Neck pain
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Tumor pain
NERVOUS SYSTEM DISORDERS – Ataxia; Dysesthesia; Lethargy; Memory impairment; Nervous system disorders - Other (burning sensation); Neuralgia; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido

decreased; Psychiatric disorders - Other (mental status changes); Psychiatric disorders - Other (mood altered)
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (bladder disorder); Renal and urinary disorders - Other (dysuria); Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Reproductive system and breast disorders - Other (genital rash)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Bronchospasm; Cough; Epistaxis; Hiccups; Nasal congestion; Postnasal drip; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (dry throat); Respiratory, thoracic and mediastinal disorders - Other (pharyngeal edema); Respiratory, thoracic and mediastinal disorders - Other (throat tightness); Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Erythema multiforme; Pain of skin; Periorbital edema; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (ephelides); Skin and subcutaneous tissue disorders - Other (madarosis); Skin and subcutaneous tissue disorders - Other (skin swelling); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Toxic epidermal necrolysis; Urticaria
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: CDX-011 (glembatumumab vedotin) (CDX-011) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
    - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
    - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

    - **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3. Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the

Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR
Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Investigations	Alanine aminotransferase	≤2	N/A	Possibly or Unrelated	90% of uveal melanoma patients on this study will have liver mets, elevated LFTs will be commonplace and are not listed on CAEPR for this drug
Investigations	Aspartate aminotransferase	≤2	N/A	Possibly or Unrelated	90% of uveal melanoma patients on this study will have liver mets, elevated LFTs will be commonplace and are not listed on CAEPR for this drug
Investigations	Blood bilirubin	≤2	N/A	Possibly or Unrelated	90% of uveal melanoma patients on this study will have liver mets, elevated LFTs will be commonplace and are not listed on CAEPR for this drug

7.4. Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.

The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete**:** Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.

7.6. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1. CDX-011 (glembatumumab vedotin), NSC 763737)

8.1.1 Classification: monoclonal IgG2 antibody (CR0111) conjugate to monomethyl-Auristatin E (MMAE)

8.1.2 CAS registry number: 1182215-65-1

8.1.3 Mode of Action:

CDX-011 combines a tumor-targeting antibody with a potent cytotoxic microtubule inhibitor, monomethylauristatin E (MMAE). The fully-human IgG2 monoclonal antibody, CR011, is directed against glycoprotein NMB (gpNMB), a transmembrane protein which is highly expressed in breast cancer and other tumors.

8.1.4 Availability / How supplied:

CDX-011 is supplied by Celldex Therapeutics and distributed by the CTEP, DCTD, NCI. CDX-011 drug product solution (injection concentrate) contains CDX-011, Sucrose NF, Histidine USP, Histidine-Hydrochloride Monohydrate EP, and Polysorbate 20 NF, at pH of 6.0 ± 0.5. It is supplied in 10 mL Clear Type-I glass vials with stoppers and aluminum crimp seals containing 50 mg per vial (5 mg/mL, 10 mL).

8.1.5 Storage:

Store intact vials at 2°-8°C (36°-46°F). The prepared dilution may be stored in the infusion bag at ambient room temperature (15 - 25°C [59 - 77°F]) for not more than 8 hours before infusion.

8.1.6 Stability: Stability of the intact vials is ongoing.

8.1.7 Route of Adinistration: IV infusion only

8.1.8 Preparation / Administration:

CDX-011 solution must be further diluted in 250 mL of 5% Dextrose. The prepared dilution is administered as an IV infusion through an in-line 0.22 micron filter over 90-minutes.

8.1.9 Dose: The starting dose of CDX-011 is 1.9 mg/kg every 3 weeks.The appropriate dose of CDX-011 should be re-calculated for each dose based on the current weight of the patient. Doses may be rounded to the nearest 0.1 mL (0.5 mg).

8.1.10 Side Effects: See CAEPR (section 7)

8.1.11 Potential Interactions:

The effect of CDX-011 on the absorption, metabolism, or excretion of other drugs has not been studied. To date, there have been no unexpected interactions observed between CDX-011

and other drugs.

In a study of a different antibody drug-conjugate containing MMAE, brentuximab vedotin, free MMAE was primarily excreted in the feces, although this represents a minor component of elimination. MMAE was also found to be metabolized by cytochrome P450 3A4 (CYP3A4) and co-administration of ketoconazole, a potent CYP3A4 inhibitor, increased MMAE exposure by approximately one-third (Adcetris [brentuximab vedotin] package insert, September 2013 and FDA Approval Package). Therefore, drugs known to strongly inhibit CYP3A4 should be used with caution while patients are exposed to CDX-011, and patients should be closely monitored for adverse reactions.

Co-administration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by almost 50%. Concomitant administration of drugs known to be potent CYP3A4 inducers should be avoided, if at all possible.

Because the concentration of free MMAE is very low, if potent CYP3A4-modifying drugs are administered concomitantly with CDX-011, dose modifications of CDX-011 are not recommended unless necessitated by toxicity.

In addition, MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp). Co- administration of brentuximab vedotin with P-gp inhibitors may increase exposure to MMAE; thus, per the brentuximab package insert (September 2013), patients who are receiving P-gp inhibitors concomitantly with brentuximab vedotin should also be closely monitored for adverse reactions.

8.1.12 Agent ordering

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time

Agent Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Agent Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Integral Laboratory or Imaging Studies

N/A

9.2. Investigational Device Information

N/A

9.3. Integrated Correlative Studies – GPNMB expression

For full details, refer to Appendices

Background

CDX-011 (glembatumumab vedotin) is an antibody-drug conjugate directed against GPNMB. Therefore, tumor expression of GPNMB is expected to correlate with response to treatment. As preliminary evidence suggests uveal melanomas highly express GPNMB (86% of samples positive)[18], patients will not be screened prior to treatment. However, to clarify pharmacodynamics of CDX-011 (glembatumumab vedotin), pre-study tumor samples as well as on-treatment tumor samples will be analyzed retrospectively for GPNMB expression. The effect of CDX-011 (glembatumumab vedotin) on GPNMB expression will be studied from the second tumor sample, and is a mandatory component for all patients on study. Patients also have the option for tissue acquisition and analysis for GPNMB at the time of progression of disease. The purpose of this biopsy is to evaluate mechanisms of resistance to treatment. There is no minimum number of patients required to undergo a biopsy at progression as information on even a modicum of patients is an opportunity to learn about resistance. ORR and PFS are expected to correlate with presence of GPNMB.

Sample Collection

- Appendix D is the lab instruction manual and submission form for acquisition, handling, and shipping of tissue specimens for GPNMB testing.
- Fax or email the completed Specimen Submittal Form located in Appendix D to Mosaic Laboratories at (949) 340-7330 (fax) or <clinicaltrials@mosaiclabs.com>.
- At some institutions, research-only biopsies may not generate formal Pathology Reports. In those cases, the reason for lack of a Pathology Report should be noted on the Specimen Submittal Form.

GPNMB Reporting

Study GPNMB result reports will not be provided to the clinical sites. All testing is performed as a per-protocol retrospective analysis. Please contact the Clinical Trial Manager with ad hoc requests for a specific patient's GPNMB test results.

Tissue Block Repatriation

All tissue blocks will be repatriated to the originating investigative site at the end of the study.

Expedited repatriation may be requested ad hoc by sites with an urgent clinical need to access the tissue block provided.

- Expedited repatriation does not extend to slides provided by investigator sites or prepared during the processing of the samples.
- When completing Specimen Submission Form, note that expedited processing is requested.
- Fax or email the completed Request Form to Mosaic Laboratories. (fax number: 949-340-7330; email: clinicaltrials@mosaiclabs.com
- Specimens for urgent/ad hoc repatriation will be shipped by Mosaic Laboratories within 10 business days from the receipt date of the samples.

9.4. Exploratory/Ancillary Correlative Studies

Immunophenotype of Patients Treated with CDX-011 (glembatumumab vedotin)

As an optional correlative endeavor, we plan to utilize metastatic tumor tissue samples at baseline and after 1 cycle of treatment (+/- 3 days) and at progression of disease to characterize the immune cell and inflammatory infiltrates in uveal melanoma tumors. We will capitalize on outstanding efforts with the MD Anderson Melanoma MoonShot Biospecimen team for tissue

acquisition and will collaborate with experienced immunology and melanoma laboratories to analyze via immunohistochemistry tumor cells for CD4, CD8, Foxp3, CD68, CD40, CD83, TGF-beta, MIF, IDO, IFN-gamma, PD-L1, iNOS, NT, Cox-2, SNO, Arginase, NFkB, pSTAT3, Bcl-2. To minimize interpersonal variations and maximize consistency, computerized barcode-driven automatic immunostainers will be used to increase precision of results.

Background and Hypothesis

The etiology behind the poor response to therapy in patients with metastatic uveal melanoma is not clear, however several factors may contribute to this. The innate immune system includes natural killer (NK) cells, granulocytes, and macrophages and is capable of inducing ocular damage. This is balanced by a variety of anti-inflammatory cytokines and scavengers of free radical species that neutralize pro-inflammatory markers. The eye has evolved to become an immune privileged organ to protect itself from damage associated with inflammation because its capacity for tissue regeneration is restricted.

The adaptive immune system, represented mainly by activated cytotoxic T-lymphocytes, is capable of recognizing viral and tumor antigens that are appropriately presented in the context of major histocompatibility complex class I (MHC I) molecules. MHC class I is expressed on normal human tissues and prevents NK-cell mediated destruction. Interestingly, MHC class I is expressed at very low levels in the eye (8, 10, 11) NK-cell mediated cytotoxic activity that is normally prompted by lack of MHC class I expression is neutralized in the eye by macrophage migration inhibitor factor (MIF) and by transforming growth factor-beta (TGF-beta). PD-L1, a member of the B7 family of membrane proteins, is expressed in the human eye and serves to down-regulate T-cell proliferation. Together, these mechanisms lead to down regulation of T cell activation and apoptosis of inflammatory cells in the microenvironment of the eye, and preserving the antigen privileged state of the eye.

Notably, 40% of tumor infiltrating lymphocytes (TIL) isolated from primary uveal melanomas express NK-cell markers. But NK-cell mediated cytolysis of uveal melanoma tumor tissue lacking MHC class I expression is inhibited by TGF-beta and MIF in the aqueous humor of the eye. Once metastatic, uveal melanomas preferentially metastasize to the liver in 90% of cases. Although the liver houses the highest concentration of NK cells in the body, which would otherwise rapidly eliminate cells lacking MHC class I expression (such as uveal melanomas), uveal melanomas have instead adopted strategies employed in the ocular environment to block NK-cell mediated cytolysis. This includes increasing MIF secretion to twice the levels of primary uveal melanoma as well as up-regulating MHC Class I expression 10-fold in comparison to primary uveal melanomas. Finally, TGF-beta2, an isoform of TGF-beta that suppresses NK cells, is expressed by metastatic uveal melanomas.

There is also evidence that uveal melanomas have an altered response to adaptive T cell-mediated immunity, though this has not been thoroughly studied. One mechanism of this is through increased indoleamine 2,3-dioxygenase (IDO) expression in the eye. T-lymphocytes are dependent upon tryptophan for their metabolism and are unable to survive in the absence of this

key building block amino acid. IDO catalyzes tryptophan degradation leading to termination of T-cell activation. IDO is expressed in many ocular tissues and is thought to be a strategy for further evasion of immune surveillance by uveal melanomas. Although IDO expression is dynamic, it is induced by interferon (IFN)-gamma exposure. Therefore, uveal melanoma cells can generate IDO in the presence of innate or adaptive immune elements such as IFN-gamma. Likewise, IFN-gamma induces expression of programmed death ligand-1 (PD-L1) on primary and metastatic uveal melanoma cell lines. PD-L1 contributes to immune privilege by interacting with its receptor PD-1 on T cells leading to down-regulation of T lymphocytes. Taken together, uveal melanoma cells are genetically programmed to respond to a pro-inflammatory environment (via IFN-gamma) and upregulate T-lymphocyte suppressive pathways such as IDO and PD-L1 to counteract immune-mediated surveillance and elimination. While this has been seen in tumors such as cutaneous melanoma and renal cell carcinoma, the mechanism of PD-L1 upregulation in uveal melanoma remains unknown.

The inflammatory microenvironment has been implicated in tumor growth in adult cancers, including melanoma. Inflammation is often induced hand-in-hand by immune cells and cytokines and chemokines which promote reactive oxygen and nitrogen species to potentiate tumor progression. Cytokine-drive inducible nitric oxide synthase (iNOS) iNOS has been shown to promote a pro-oxidant and pro-inflammatory state in melanoma. Expression of iNOS in vivo is prognostic of poor survival as patients whose melanomas express higher levels of iNOS have decreased survival. Reactive oxygen and nitrogen species react with proteins intra-tumorally via S-nitrosylation (SNO) and nitration of tyrosines (NT). This post-translational modification of proteins is irreversible and can alter antigenicity. For example, nitrosylation of the MHC Class I receptor inhibits presentation of tumor antigen to cytotoxic T lymphocytes. NF-kB represents another pro-inflammatory cancer target gene where tumor cell cytotoxicity is related to NF-kB expression. NF-kB inhibits anti-oxidation and activates anti-apoptotic genes (Bcl-2) in addition to upregulating other factors involved in metastasis such as angiogenesis and expression of of immunosuppressive mediators (Arginase, Cox-2, STAT3 activation).

Based on the immune privilege of the eye and the low level of cytotoxic T cell infiltrate in primary uveal melanomas associated with elevated inhibitory cytokines TGF-beta and MIF, we expect a similar infiltrate in metastatic uveal melanomas where we mechanisms for immune evasion likely persist. Immunphenotype in metastatic tumor tissue is expected to be of low cytotoxic T cell quantity with high inhibitory, regulatory, and inflammatory markers. Markers to be evaluated include, but are not limited to: CD4, CD8, Foxp3, CD68, CD40, CD83, TGF-beta, MIF, IDO, IFN-gamma, PD-L1, iNOS, NT, Cox-2, SNO, Arginase, NFkB, pSTAT3, Bcl-2.

Tissue quality will be variable in metastatic tumors as they will consist mainly of core needle biopsies from various metastatic sites. To address this, all slides will undergo path quality control by a dermatopathologist, and areas of viable tumor will be circled on each slide.

This work is currently funded by a peer-reviewed institutional research grant to investigate differential immunophenotypes in uveal melanoma. Preliminary data is from the grant is not currently available.

Methods

For this optional exploratory correlative analysis, MD Anderson Cancer Center (MDACC) patients will be co-consented to protocol 2012-0846, a laboratory collection and use protocol entitled "Longitudinal biopsy tissue acquisition protocol" or awarded institutional funds will be used to cover biopsy costs. Non-MDACC sites will obtain tissue for optional correlative studies per local institutional guidelines. Archival tissue at baseline in the form of formalin-fixed, paraffin-embedded tumor tissue can be utilized. On-treatment optional tumor tissue will be obtained after the first cycle of treatment (+/- 3 days) and can be piggybacked onto the mandatory clinical trial biopsy that occurs at this timepoint for GPNMB expression. At progression of disease, patients have the option to undergo another tumor biopsy for correlative studies. Tissue may be obtained via incisional biopsy, excisional biopsy, core needle biopsy, or fine needle aspiration.

These tumor samples will be analyzed via immunohistochemistry for the following markers: CD4, CD8, Foxp3, CD68, CD40, CD83, TGF-beta, MIF, IDO, IFN-gamma, PD-L1, iNOS, NT, Cox-2, SNO, Arginase, NFkB, pSTAT3, Bcl-2. The relative percentages and changes in of these immune infiltrates will be descriptively summarized. IntelliPATH FLX™ Automated Slide Staining System will be used to perform immunohistochemistry. This system increases the reproducibility of results using barcode-drive immunostainers to dispense reagents, control washing, mixing, heating, and to optimize reaction kinetics. This system is compatible with reagents from any source, thereby increasing ease of use, and is currently utilized in MDACC laboratories. RT-PCR will be used to monitor cytokine expression in the tumor microenvironment. Flow cytometry-based analysis will used to monitor the population of cytokine producing T cells.

Collection of Specimens(s)

Metastatic tumor tissue will be collected at baseline (archival tissue is allowed) as well as after the first cycle of treatment (+/- 3 days). Core biopsies will be performed using a 21-gauge needle or institutional protocol for safe tissue acquisition.

Handling of Specimens(s)

a. Tissue will be fixed in 10% neutral buffered formalin and embedded in paraffin per local procedures.
b. Samples will be adhered as 4-µm sections to glass slides (no minimum or maximum number of slides are required).
c. Slides will be evaluated by a dedicated dermatopathologist who will identify areas of viable tumor tissue.

Shipping of Specimen(s)

- Where available, include a Pathology Report with the sample.
- Black out subject identifiers such as name, address, telephone number, and social security

number on the Pathology Report. Do not black out Accession number, date of birth, age, date of specimen collection, site of specimen collection.

- Label slides with pathology Accession number, date slides were cut, subject initials, CTSU subject number.
- Email ClinicalResearchSupport@mdanderson.org to report shipping of slides.
- Package and ship slides in accordance with local institutional policies and procedures. Please use frozen gel packs for instances of extreme heat. The shipping address for optional correlative study specimens is:

  Sapna Patel, M.D.
  MD Anderson Melanoma Oncology
  Attention: NCI9855 / CDX011 study
  1515 Holcombe Blvd, Unit 0430
  Houston, TX 77030

Site(s) Performing Correlative Study

MD Anderson Cancer Center will perform the correlative studies described in this section.

Statistical Analysis

The relative percentages of immune and inflammatory infiltrates will be descriptively summarized by a dedicated dermatopathologist for each time point. Paired t-tests or Wilcoxon signed-rank tests will be used to compare infiltrate percentages by time point. In addition, the levels of infiltrates from each time point and the change in infiltrate between time points will be compared with clinical outcomes such as time to progression using Kaplan-Meier survival curves, Cox proportional hazards regression, and t-tests or Wilcoxon rank sum tests.

If possible, two group t-tests or Wilcoxon rank sum tests will be used to compare infiltrates by tissue type (hepatic, extra-hepatic) or by gene expression profile, if that data is available about the primary uveal melanoma

Correlation of Rash with Clinical Benefit

Background and Hypothesis

In the melanoma Phase I/II study CR011-CLN-11, development of rash of any grade, which may be related to the presence of GPNMB in the skin, within the first 21 days of treatment was associated with greater PFS and ORR.[18] Patients who developed rash in cycle 1 had a median PFS of 4.4 months compared with PFS of 1.3 months in patients who did not develop a rash (HR 0.37, *P*=0.001). Rash also correlated with prolonged PFS in the Phase II breast cancer study (EMERGE), although this correlation was not observed in the earlier Phase I/II breast cancer study (CR011-CLN-20).[19] For this study, we expect development of rash in cycle 1 will similarly correlate with improvement in PFS and ORR.

Methods

All patients who receive 1 dose of study drug will be followed for development of rash. Rash of any type and any grade that develops at any time during treatment will be captured.

Collection of Specimen(s)
N/A

Handling of Specimens(s)
N/A

Shipping of Specimen(s)
N/A

Site(s) Performing Correlative Study

MD Anderson Cancer Center will perform the correlative studies described in this section.

Statistical Analysis

Descriptive statistics will be used to report the development and grade of rash in patients on treatment, with particular attention to development of rash during cycle 1. Wilcoxon rank sum, Cox proportional hazards regression, and Kaplan-Meier survival curves will be used to correlate rash and/or severity with PFS and ORR.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	C1 Wk 1	C1 Wk 2	C1 Wk 3	C2 Wk 4[d]	C2 Wk 5	C2 Wk 6	C3 Wk 7	C3 Wk 8	C3 Wk 9	C 4[g] Wk 10	C4[g] Wk 11	C4[g] Wk 12	Off Study Treatment[c]	Survival follow-up
CDX-011 (glembatumumab vedotin)		X			X			X			X				
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	Assessed at the beginning of each cycle													
Physical exam	X	X			X			X			X			X	
Vital signs	X	X			X			X			X			X	
Height	X														
Weight	X	X			X			X			X			X	
Performance status	X	X			X			X			X			X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event evaluation		Assessed at the beginning of each cycle and as they emerge or are reported												X	
Tumor measurements	X	Tumor measurements are repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X	
Radiologic evaluation	X	Radiologic measurements should be performed every 6 weeks.												X	
B-HCG	X[b]														
Tumor tissue (archival for Pre-Study is acceptable) for	X			X[e]										X (optional)	

GPNMB expression by IHC															
Optional correlative studies	X			X[e]										X (optional)	
Documentation of vital status															X[f]
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. b: Serum pregnancy test (women of childbearing potential). c: To be performed within 30 days of last treatment dose. d: Cycle 2 and beyond infusions and assessments have a window of +/- 3 days. If treatment is delayed, labs and other assessments are valid if performed within 3 days of treatment. e: On-treatment tumor biopsy can occur at the end of Week 3 just prior to beginning Cycle 2, +/- 3 days. f: Patients will be followed for at least 30 days after discontinuation of study treatment or until death, whichever comes first. Subsequently, vital status will be extracted from the medical chart or public records, where available. g. Subsequent cycles will have the same schedule as Cycle 4															

11. MEASUREMENT OF EFFECT

11.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with CDX-011 (glembatumumab vedotin).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions

with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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 is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at

baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT 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 the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. 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.

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. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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 (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.
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.

c. 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. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: 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.

Response Criteria

Evaluation of Target Lesions

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 (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesion	Non-Target	New Lesion	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Confirmation not required for Protocol 9855.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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 the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.2. Other Response Parameters

N/A

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the

appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.2. CTEP Multicenter Guidelines

N/A

12.3. Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can

Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-

Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

This trial is a single-arm, open-label Phase II study of CDX-011 (glembatumumab vedotin) in patients with metastatic uveal melanoma. The primary endpoint is overall response rate (ORR) using RECIST 1.1. Secondary endpoints include GPNMB expression, progression-free survival (PFS), overall survival (OS), safety and toxicity. Exploratory endpoints include characterizing the anti-tumor immunophenotype of patients receiving CDX-011 (glembatumumab vedotin) as well as post-hoc correlation of rash with PFS and ORR. Simon's two-stage design will be used to monitor the primary endpoint.

All patients who receive study drug will be eligible for evaluation of the primary endpoint of ORR. All patients who receive study drug will also be evaluated for secondary endpoints of PFS, OS, safety, toxicity, and GPNMB expression.

Toxicity will be reported by type, frequency, and severity according to the NCI Common Toxicity Criteria v5.0. All patients who receive any amount of study drug will be evaluable for toxicity.

13.2. Sample Size and Power /Accrual Rate

The historical response rate to metastatic treatments in this population is 5%. We will target a 24% ORR in GPNMB-positive patients. We expect the ORR in GPNMB-negative patients to be close to zero, and we assume 15% of uveal melanoma patients will be GPNMB-negative based on prior evidence.[15] Thus, overall we will target a (0.24 * 85%) + (0 * 15%) = 20% ORR. We will use a Simon's two-stage design.[22] In the first stage, 18 evaluable patients will be enrolled

and assessed for response. If no responses are seen, the study will stop and reject CDX-011 (glembatumumab vedotin) for further study in this population. If at least 1 response is seen, the study will proceed with stage 2 where 14 additional patients will be enrolled and evaluated for response. For logistical purposes, after 18 patients have been enrolled, Stage 2 will not begin until at least one patient has experienced a response. At the end of the trial, if at least 4 patients have an objective response, the trial will be declared a success, and CDX-011 (glembatumumab vedotin) will be considered for future study. If 3 or fewer patients have an objective response, the drug will be rejected.

If the true ORR is 5%, the probability that the study terminates after the first stage is 39.7%, and the probability that the drug is incorrectly considered for future study (Type I error) is 7.2%. If the true ORR is 20%, the probability that the drug is incorrectly rejected (Type II error) is 9.8%

Patients will be enrolled at MD Anderson Cancer Center at an expected rate of 2-3 patients per month. 32 evaluable patients are needed for statistical analysis in Stage 1 and Stage 2. Allowing for attrition of patients who do not remain on study long enough to be evaluable for the primary endpoint, the maximum enrollment for this study will be 35 patients.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	1	0	0	**1**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	1	0	**1**
White	15	17	0	1	**32**
More Than One Race	0	0	0	0	**0**
Total	**15**	**18**	**1**	**1**	**35**

13.3. Stratification Factors

N/A

13.4. Analysis of Secondary Endpoints

Analysis of secondary endpoints will be exploratory and hypothesis-generating. For secondary endpoints, all eligible patients will be included in the analyses.

GPNMB expression

GPNMB IHC will be performed retrospectively on baseline tumor tissue in all patients included on study. GPNMB IHC will also be performed on tumor tissue on all patients at Day 21 on study. Changes in percentage of GPNMB-positive tumor cells will be reported and descriptive statistics will be used to further report staining intensity and frequency in baseline and on-treatment tumor samples.

In testing the analytical performance and precision of GPNMB IHC, sections from 3 human melanoma tissues and 2 cell lines were stained in 6 replicates on a single batch and scored by one pathologist. The differences in percentage of the stained cells ranged from 0-6%.

Because samples from this study are going to be analyzed retrospectively in one batch and scored by the same pathologist, a change in GPNMB expression greater than 10% will be considered a positive signal.

Progression-free survival (PFS) overall survival (OS).

PFS and OS survival curves will be calculated using the method of Kaplan-Meier. Median PFS and OS will be reported with 95% confidence intervals. All patients who receive study drug will be followed for PFS and OS.

Safety Analysis

Toxicity will be reported by type, frequency, and severity according to the NCI Common Toxicity Criteria.

Toxicity will be continuously monitored in all patients who receive study drug and reported in real time to the local PI as the study team is made aware. Toxicity will also be reviewed at monthly protocol meetings at each enrolling site. If multiple sites register patients, a monthly teleconference will be scheduled to review safety and toxicity in aggregate as well as patient outcomes.

13.5. Reporting and Exclusions

Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with CDX-011 (glembatumumab vedotin).

Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. If a patient does not receive study drug, then he or she will not be evaluated for ORR, PFS, OS, GPNMB expression, safety, or toxicity and the position in statistical analysis will be replaced by an evaluable patient. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES

1. Singh AD, Topham A. Survival rates with uveal melanoma in the United States: 1973-1997. Ophthalmol. 2003; 110(5):962-65.
2. Lorigan JG, Wallace S, Mavligit GM. The prevalence and location of metastases from ocular melanoma: imaging study in 110 patients. Am J Roentgenol. 1991; 157(6):1279-81.
3. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. Arch Ophthalmol 2001; 119(5):670-6.
4. Collaborative Ocular Melanoma Study Group. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study (COMS) Group Report No. 26. Arch Ophthalmol. 2005; 123(12):1639-43.
5. Sato T, Han F, Yamamoto A. The biology and management of uveal melanoma. Curr Oncol Rep. 2008; 10(5):431-8.
6. Mariani P, Piperno-Neumann S, Servois V, Berry MG, Dorval T, Plancher C et al. Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2009; 35(11):1192-7.
7. Bedikian AY, Legha SS, Mavligit G, Carrasco CH, Khorana S, Plager C et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. Cancer. 1995; 76(9):1665-70.
8. Bedikian AY, Papadopoulos N, Plager C, Eton O, Ring S. Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma research. 2003; 13(3):303-6.
9. Vuoristo MS, Hahka-Kemppinen M, Parvinen LM, Pyrhonen S, Seppa H, Korpela M et al. Randomized trial of dacarbazine versus bleomycin, vincristine, lomustine and dacarbazine (BOLD) chemotherapy combined with natural or recombinant interferon-alpha in patients with advanced melanoma. Melanoma research. 2005; 15(4):291-6.
10. Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA 2014; 311(23): 2397-2405.
11. Hofmann UB, Kauczok-Vetter CS, Houben R, Becker JC. Overexpression of the KIT/SCF in uveal melanoma does not translate into clinical efficacy of imatinib mesylate. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15(1):324-9.
12. Mahipal A, Tijani L, Chan K, Laudadio M, Mastrangelo MJ, Sato T. A pilot study of sunitinib malate in patients with metastatic uveal melanoma. Melanoma research. 2012; 22(6):440-6.
13. Tse KF, Jeffers M, Pollack VA, McCabe DA, Shadish ML, Khramtsov NV, et al. CR011, a fully human monoclonal antibody-auristatin E conjugate, for the treatment of melanoma. Clin Cancer Res. 2006; 12(4):1373-82.
14. Qian X, Mills E, Torgov M, LaRochelle WJ, Jeffers M. Pharmacologically enhanced expression of GPNMB increases the sensitivity of melanoma cells to the CR011-vcMMAE antibody-drug conjugate. Mol Oncol. 2008; 2(1):81-93.
15. Williams MD, Esmaeli B, Soheili A, Simantov R, Gombos DS, Bedikian AY, Hwu P. GPNMB expression in uveal melanoma: a potential for targeted therapy. Melanoma

Research 2010; 20:184–190.
16. Naumovski L, Junutula JR. Glembatumumab vedotin, a conjugate of an anti-glycoprotein non- metastatic melanoma protein B mAb and monomethyl auristatin E for the treatment of melanoma and breast cancer. Curr Opin Mol Ther. 2010; 12(2):248-57.
17. Pollack VA, Alvarez E, Tse KF, Torgov MY, Xie S, Shenoy SG, et al. Treatment parameters modulating regression of human melanoma xenografts by an antibody-drug conjugate (CR011- vcMMAE) targeting GPNMB. Cancer Chemother Pharmacol. 2007; 60(3):423-35.
18. Ott PA, Hamid O, Pavlick AC, Kluger H, Kim KB, Boasberg PD et al. Phase I/II Study of the Antibody-Drug Conjugate Glembatumumab Vedotin in Patients With Advanced Melanoma. J Clin Oncol. 2014; 32(32):3659-66.
19. Bendell J, Saleh M, Rose AA, Siegel PM, Hart L, Sirpal S et al. Phase I/II study of the antibody-drug conjugate glembatumumab vedotin in patients with locally advanced or metastatic breast cancer. J Clin Oncol. 2014; 32(32):3619-25.
20. Frederick DT, Piris A, Cogdill AP, Cooper ZA, Lezcano C, Ferrone CR et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res. 2013; 19(5):1225-31.
21. Cooper ZA, Juneja VR, Sage PT, Frederick DT, Piris A, Mitra D et al. Response to BRAF inhibition in melanoma is enhanced when comined with immune checkpoint blockade. Cancer Immunol Res. 2014; 2(7):643-54.
22. Thall PF, Simon R, Ellenberg SS, Shrager R. Optimal two-stage designs for clinical trials with binary response. Stat Med. 1988; 7(5):571-9.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient_____is enrolled on a clinical trial using the experimental agent **CDX-011 (glembatumumab vedotin)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

CDX-011 (glembatumumab vedotin) interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

CDX-011 (glembatumumab vedotin) interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is/are **CYP3A4**, and CDX-011 (glembatumumab vedotin) is broken down by this enzyme in order to be cleared from your system.
- CDX-011 (glembatumumab vedotin) must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**.
- Your prescribers should consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking CDX-011 (glembatumumab vedotin).
    - If you take the blood thinner warfarin. INR levels may be affected by concomitant administration of warfarin with CDX-011 (glembatumumab vedotin). Additionally, the effectiveness of CDX-011 (glembatumumab vedotin) may be affected by warfarin metabolism.
    - If you take antifungals such as ketoconazole as these medicines lead to decreased levels of CDX-011 (glembatumumab vedotin) and may result in decreased anti-tumor activity.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

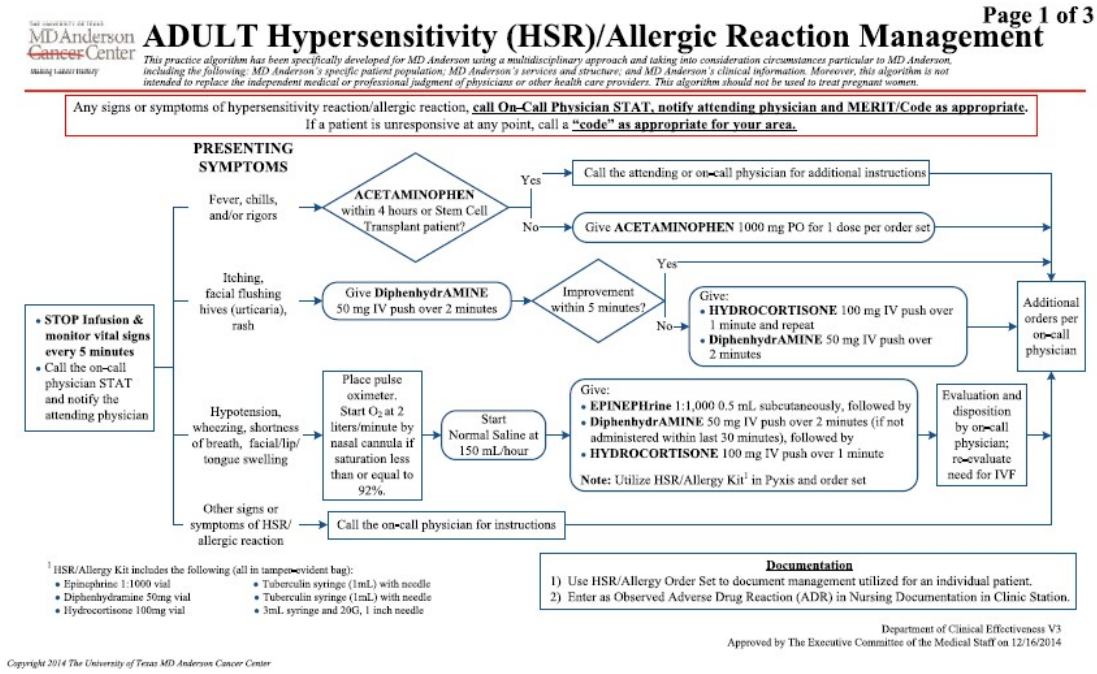
_____

and he or she can be contacted at

_____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial using the experimental agent **CDX-011 (glembatumumab vedotin).** This clinical trial is sponsored by the NCI. **CDX-011 (glembatumumab vedotin)** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking	**CDX-011 (glembatumumab vedotin)** interacts with a specific liver enzyme called **CYP3A4** and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will record any medicines you take that are considered "strong inducers/inhibitors or substrates of **CYP3A4.**" ➢ Before prescribing new medicines, your

APPENDIX C ADULT HYPERSENSITIVITY/ALLERGIC REACTION MANAGEMENT ALGORITHM



MD Anderson Cancer Center
Making Cancer History

ADULT Hypersensitivity (HSR)/Allergic Reaction Management

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

SUGGESTED READINGS

Gomes E.R. & Demoly P. (2005). Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol*, 5, 309-316
Lenz, H.J. (2007). Management and Preparedness for Infusion and Hypersensitvity Reactions. *The Oncologist*, 21, 601-609.
Lieberman, P., Kemp, S.F., Oppenheimer, J., & et al. (2007) The diagnosis and management of anaphylaxis: An updated practice parameter. *Journal of Allergy and Clinical Immunology, (115)*, 3, 483-523.
Rushton, F.A. (2007). Recognition and management of patients with anaphylaxis. *Nursing Standards, (21)*, 37, 50-57.
Zanotti K.M. & Markman, M. (2001). Prevention and management of antineoplastic induced hypersensitivity reactions. *Drug Safety*, 24, 767-779.

Department of Clinical Effectiveness V3
Approved by The Executive Committee of the Medical Staff on 12/16/2014

MD Anderson Cancer Center
Making Cancer History®

ADULT Hypersensitivity (HSR)/Allergic Reaction Management

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

DEVELOPMENT CREDITS

This practice consensus algorithm is based on majority expert opinion of the Adult Hypersensitivity work group at the University of Texas M.D. Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following experts:

Carmen Escalante, MD
Susan Gaeta, MD
Huifang "Linda" Lu, MD, PhD
Wenli Liu, MD
Ellen Manzullo, MD
Laura Michaud, PhD, PharmD, RPH
Rina Patel, PharmD, RPh
Goley Richardson, BSN, RN, OCN
Leonard Roes, PharmD, RPh

[F] Core Development Team Leader

Department of Clinical Effectiveness V3
Approved by The Executive Committee of the Medical Staff on 12/16/2014

APPENDIX D INSTRUCTION MANUAL AND SPECIMEN SUBMISSION FORM

MOSAIC LABORATORIES

INSTRUCTION MANUAL
CDX011-51 / P9855
Archival Tumor Sample Collection

Mosaic Laboratories
Attention: Clinical Trials
12 Spectrum Pointe Drive
Lake Forest, CA 92630

Phone: (949) 340-7598
Fax: (949) 340-7330
clinicaltrials@mosaiclabs.com

CLIA ID# 05D1059086
Eric Olsen, M.D. Medical Director

1.0 PURPOSE

This instructional guide is supplied to facilitate the proper acquisition and handling of human tissue specimens for shipment to Mosaic Laboratories for NCI clinical trial P9855/CDX011-51. These instructions define the types of specimens, how to process the specimen samples, and how to ship the samples to Mosaic Laboratories.

2.0 SCOPE

This instructional guide pertains to institutions enrolling subjects who have given consent to obtain specimens for the study P9855/ CDX011-51. The specimens are to be sent to Mosaic Laboratories. These procedures and guidelines should be followed to ensure that only high quality human specimens are obtained. Any personnel involved with the processing of these specimens should read, understand and follow these instructions.

3.1 MATERIALS PROVIDED BY MOSAIC LABORATORIES

- Specimen Submittal Form (Appendix A)

4.1 MATERIALS PROVIDED BY SITE

- At least 10 positive-charged glass slides
- Shipping Materials
- Microtome
- Blade
- Waterbath

5.0 SPECIMEN PREPARATION

5.1 Only specimens obtained from a patient being screened for inclusion into and/or participating in CDX011-51 / P9855 and consented to specimen collection may be submitted to Mosaic Laboratories.

5.2 Obtain and handle human paraffin material using standard of care technique and universal precautions. Appropriate care should be taken to preserve the integrity of the samples.

6.0 PROCEDURE FOR ARCHIVAL TUMOR SECTIONING

6.1 Ten (10) sections should be cut at 4 to 5 microns using a clean waterbath. Do not add any adhesives to the waterbath. Please use positively-charged slides.

6.1.1 Clean waterbath: A kimwipe should be placed on top of the water to collect any remaining fragments of tissue and paraffin in between each sample. This will help to prevent any carryover of other tissue that might stick to the slide.

6.1.2 Please ensure that each specimen submitted contains predominantly tumor tissue.

6.1.3 Position the section in the center of the slide, one section per slide.

6.1.4 Drain excess water from slide by standing slide vertically on a paper towel until water runs down to the bottom.

6.1.5 Gently tap slide on paper towel to remove any excess water.

6.1.6 Slides should air dried only.

6.1.7 Provide 10 slides for analysis. 3-4 slides will be used for prospective IHC staining and 6-7 slides will be retained for retrospective PCR analysis to assess correlation between IHC and PCR methods of gpNMB detection. In cases where 10 slides are not available, at least 4 slides must be submitted for analysis.

6.2 **The corresponding Pathology Report must be submitted along with every specimen, labeled with the Subject number and the Block ID.**

6.2.1 Pathology specimens without an accompanying Pathology Report are considered incomplete. Ensure the local pathology accession number (block ID) is visible and legible on the tumor block or specimen submission and that slides are labeled with the block ID of the originating block.

6.2.2 Circle or underline the pathology accession number and block ID on the pathology report for the pathology specimens submitted. Submit a copy of the corresponding **Pathology Report.**

6.2.3 Black out the subject identifiers on the pathology report such as name, address and social security number. **DO NOT:** black out/remove information such as pathology accession number, date of birth, age, date of specimen collection, etc. *Verify that the pathology accession number and block ID has been circled or underlined on the report.*

6.3 **Patient Identification for slides**

6.3.1 All slides made from the block should be labeled with the local pathology accession number (Block ID), date slides were cut (if space permits), subject number, patient DOB, and patient initials (not the patient name). Unlabeled slides will be rejected.

7.0 DOCUMENTATION

7.1 **Specimen Submittal Form**

7.1.1 Ensure each specimen is appropriately labeled.

7.1.2 Complete one **Specimen Submittal Form** per specimen.

7.1.3 FAX or email as directed on the form.

7.1.4 Include a copy of the pathology report for each block (if available).

7.1.5 Complete a shipping Airbill (not provided). The tracking number will need to be manually written on the Specimen Submittal Form.

8.0 PACKAGING AND SHIPPING ARCHIVAL TUMOR SLIDES

8.1 NOTE: Tumor samples should be shipped on Monday through Friday using overnight shipping. Tumor Tissue may be shipped for Saturday Delivery. Mosaic Laboratories does not accept deliveries on the following US holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, and Christmas Day.

8.2 Complete the Specimen Submittal Form (**Appendix A**) to accompany the slides.

8.3 Fax or email the completed Specimen Submittal Form (**Appendix A**) to Mosaic Laboratories. (fax number: 949-340-7330; email: clinicaltrials@mosaiclabs.com).

8.3.1 **IMPORTANT:** For tracking purposes, email or fax the **Specimen Submittal Form** (Appendix A) the day the samples are sent.

8.4 Package and ship samples in accordance with institutional procedures. The shipping address is:

Mosaic Laboratories
Attention: Clinical Trials (CDX011-51 / P9855)
12 Spectrum Pointe Drive
Lake Forest, CA 92630

8.5 Please use frozen gel packs in cases of extreme heat.

8.5.1 Ensure the gel packs have been frozen for at least 24 hours.

8.5.2 All slide samples and paraffin blocks should be shipped ambient. However during extreme heat (e.g. ambient temperature exceeding 90˚F or during warm summer months), samples should be shipped with a cold pack placed inside the box, between the instruction panel and the box lid.

8.6 While waiting for pick-up, packages should be protected from temperature fluctuations (direct sunlight or outside loading docks), as fluctuations in temperature may affect immunostaining results.

9.0 QUESTIONS

9.1 For questions relating to sample collection, please call Mosaic Laboratories (949-340-7598) or email clinicaltrials@mosaiclabs.com and reference your clinical trial (CDX011-51 / P9855). The project manager for this study is Lisa Dauffenbach (primary).

10.0 REPORTING RESULTS

10.1 Samples will be analyzed in batches at Mosaic Laboratories. Mosaic Laboratories will provide gpNMB staining results to MD Anderson (lead investigator) upon request.

10.1.1 If the tissue does not contain tumor, the site will be notified immediately so that additional tissue may be procured.

MOSAIC LABORATORIES

INSTRUCTION MANUAL
CDX011-51 / P9855
Archival Tumor Sample Collection

Mosaic Laboratories
Attention: Clinical Trials
12 Spectrum Pointe Drive
Lake Forest, CA 92630

Phone: (949) 340-7598
Fax: (949) 340-7330
clinicaltrials@mosaiclabs.com

CLIA ID# 05D1059086
Eric Olsen, M.D. Medical Director

Appendix A: Specimen Submittal Form

Please complete form and FAX or Email to: FAX: (949) 340-7330; Email: clinicaltrials@mosaiclabs.com

Please include the following in the subject line: CDX011-51 / P9855

SITE TO COMPLETE THIS SECTION; COMPLETE ONE FORM PER SPECIMEN

HUMAN SUBJECT INFORMATION

Site / Subject Number	Date of Birth	Subject Initials	Gender
☐☐☐☐☐☐☐☐☐☐	_____ - _____ - _____ Day Month (3 letters) Year	___-___- First – Middle - Last	☐ Male ☐ Female

CLINICAL SITE INFORMATION

Primary Contact (Name / Phone / Email):	Address:

TUMOR SAMPLE AND SHIPPING INFORMATION

☐ Tissue Slides; Qty: _____ **(Minimum of 10, positive charged required)**	**Pathology Report included?** ☐ Ye ☐ s	**Block ID or Slide ID**	**Timeframe of Tissue Collection:** ☐ Archival

Tumor Type	Tumor Site	Body Site	Collection Date	Collection Method	Date of Sectioning
☐ Uveal Melanoma	☐ Primary ☐ Metastatic			☐ Core biopsy ☐ Excision biopsy ☐ Resection ☐ Other specify: _____	

Comments	Shipping Condition:

Date of Shipment	Tracking Number	Person Responsible

MOSAIC LABORATORIES TO COMPLETE THIS SECTION

SPECIMEN RECEIPT & PROCESSING		
Specimen Condition: ☐ Good ☐ Other: _____ Mosaic ID: _____	**Shipper Kit Contents:**	
Date/Time/Initials Processed:	**Comments:**	**QC Initials/Date:**