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CHILDREN'S ONCOLOGY GROUP

AOST1521

A Phase 2 Study of GPNMB-targeted Antibody-Drug Conjugate, CDX-011 (Glembatumumab Vedotin, CR011-vcMMAE; IND# 128248, NSC# 763737), in Recurrent or Refractory Osteosarcoma

An Intergroup NCTN Phase 2 Study

NCI Supplied Agent: CDX-011 (IND# 128248, NSC# 763737)

IND Sponsor for CDX-011: DCTD, NCI

STUDY CHAIR

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Participating Organizations

COG / Children's Oncology Group

ALLIANCE / Alliance for Clinical Trials in Oncology

ECOG-ACRIN / ECOG-ACRIN Cancer Research Group

NRG / NRG Oncology

SWOG / SWOG

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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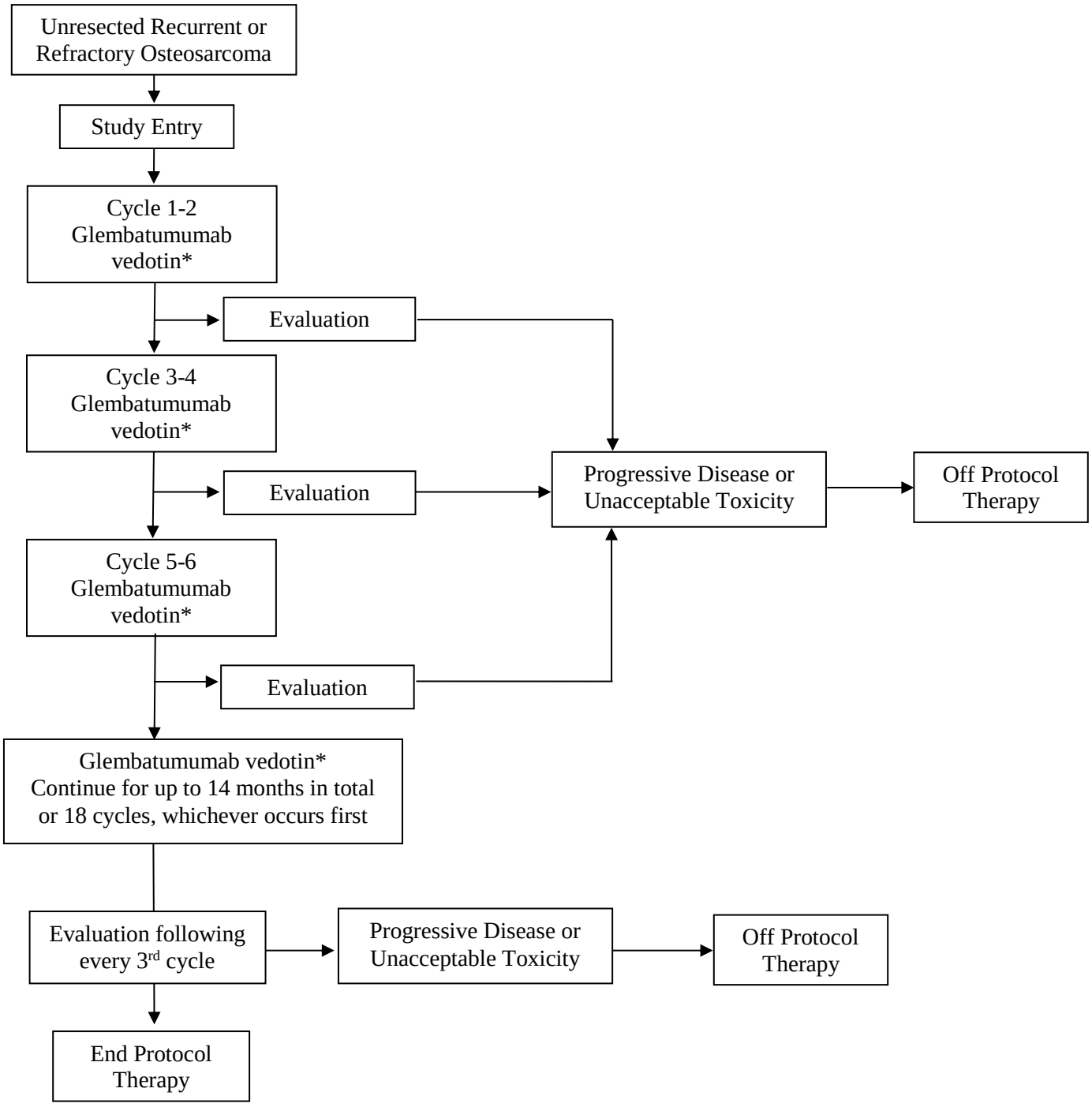
SEE SECTION 15.0 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

The prognosis of patients with recurrent or refractory osteosarcoma remains poor, with 10-year overall survival rates around 20%. Given the continued poor prognosis in this group of patients, novel treatment strategies are needed. There are no standard chemotherapeutic agents or targeted therapies proven to prolong survival in recurrent osteosarcoma. Glycoprotein non-metastatic B (GPNMB) is a type I transmembrane glycoprotein that is normally expressed in a variety of cell types including osteoblasts and osteoclasts, dendritic cells, macrophages, hematopoietic cells, melanocytes and keratinocytes. Aberrant and over expression of GPNMB has been demonstrated in a variety of cancers including osteosarcoma. GPNMB is predominantly expressed on the cell surface of malignant cells, whereas in normal tissues it is generally restricted to intracellular compartments. This unique expression pattern makes GPNMB an attractive target for antibody drug conjugate (ADC) targeted therapy. CDX-011 is an ADC directed against GPNMB. It is comprised of a fully-human IgG2 monoclonal antibody (CR011) conjugated to the potent microtubule inhibitor, monomethyl auristatin E (MMAE), via a protease-sensitive valine-citrulline peptide linker and p-aminobenzoic acid (PABA) spacer. CDX-011 is theorized to exert its antitumor activity by selectively delivering the potent cytotoxin MMAE to GPNMB-expressing tumor cells. Pre-clinical data suggest that CDX-011 may have anti-tumor activity in osteosarcoma. In this Phase 2 study, eligible patients between the ages of 12 months and 50 years with unresected, recurrent or refractory osteosarcoma will receive CDX-011, administered once every 21 days for up to 14 months. Progression free survival and response to therapy will be assessed. In addition, the tolerability and pharmacokinetic (PK) disposition of CDX-011 will be evaluated.

EXPERIMENTAL DESIGN SCHEMA



*Glembatumumab vedotin will be given on Day 1 of each 21-day cycle

Note: Patients who undergo surgical resection of or radiation to any site of measurable disease prior to completion of the 6th cycle of therapy will be taken off protocol therapy.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate whether CDX-011 therapy either improves the disease control rate at 4 months in patients with recurrent measurable osteosarcoma as compared to an historical COG experience or produces an objective response rate in patients without previous eribulin treatment.

1.2 Secondary Aims

1.2.1 To assess the feasibility and toxicity profile of CDX-011 in patients with recurrent osteosarcoma.

1.2.2 To describe the pharmacokinetics of CDX-011 in adolescents and young adults with recurrent osteosarcoma enrolled at COG sites and COG Phase 1 Consortium sites only.

1.2.3 To determine if there is a relationship between tumor GPNMB expression by IHC and response to CDX-011 therapy.

1.2.4 To estimate, in the cohort of patients previously treated with eribulin, the proportion who will experience disease progression during the first 4 months of CDX-011 therapy and the proportion of patients who experience a RECIST-defined complete or partial response.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number.

COG sites: This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

Non-COG sites: Fax the patient registration information (demography) to the Cancer Trials Support Unit (CTSU) registrar at 1-888-691-8039. Sites may notify the registration office of an incoming fax by calling 1888-462-3009; the office hours are 9:00 – 5:30 pm Eastern Time, Monday – Friday. The CTSU registrar will then register the patient within the COG system on behalf of the institution and obtain a COG patient ID number. The CTSU registrar will provide the COG patient ID number to the site which can then enroll the patient in the OPEN system.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and CTSU Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
E-mailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: 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. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. 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 (ie, laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing

protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **seven (7)** business days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase 2 study prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

Institutions are advised to plan ahead to ensure adequate and timely delivery of the investigational agent (see Section 6.1 for details).

3.1.6 Participation in Biology Studies

In order to minimize the potential for non-compliance once enrolled, patients/guardians must be made aware that some of the biology research studies are mandatory and understand that a number of non-standard blood samples will be required.

3.1.7 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 4.2.1 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

Patients must be equal to or greater than 12 years of age but less than 50 years of age at the time of enrollment.

3.2.2 Diagnosis

3.2.2.1 Patients must have had histologic verification of osteosarcoma at original diagnosis or relapse.

3.2.2.2 Patients must have measurable disease according to RECIST 1.1 (see Section 10.2), and have relapsed or become refractory to conventional therapy.

3.2.3 Specimen Submission

Patient must have archival tumor specimen available for submission (see Section 15.1).

3.2.4 Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.5 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study (4 weeks if prior nitrosourea).

b. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.

c. Radiation therapy (RT): ≥ 2 weeks for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if ≥ 50% radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial BM radiation.

d. Monoclonal antibodies: Must not have received any monoclonal based therapies within 4 weeks, and all other immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) within 2 weeks, prior to study enrollment.

Please see Section 4.1.1 for the concomitant therapy restrictions for patients during treatment.

3.2.6 Organ Function Requirements

3.2.6.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 75,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

3.2.6.2 Adequate Renal Function Defined As:
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[50] utilizing child length and stature data published by the CDC.

3.2.6.3 Adequate Liver Function Defined As:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 110 U/L. For the purposes of this study the ULN for SGPT is defined as 45 U/L.
- Serum albumin > 2 g/dL

3.2.6.4 Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.7 Exclusion Criteria

3.2.7.1 Patients with > Grade 2 neuropathy according to the Modified ("Balis") Pediatric Scale (see Section 5.2.4) of Peripheral Neuropathies will be excluded except in cases in which neuropathy is secondary to prior surgery.

3.2.7.2 Patients who have previously received CDX-011 (CR011-vcMMAE; CDX-011) or other MMAE-containing agents.

3.2.7.3 Patients who have received other investigational drugs within 2 weeks or 5 half-lives (whichever is longer) prior to study enrollment.

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

3.2.7.5 Patients with known central nervous system metastasis are not eligible.

3.2.7.6 Patients who have had major surgery within 2 weeks prior to enrollment are not eligible. Procedures such as placement of a central vascular catheter, or limited tumor biopsy, are not considered major surgery.

3.2.7.7 Pregnancy and Breast Feeding

3.2.7.7.1 Female patients who are pregnant are ineligible since there is yet no available information regarding human fetal or teratogenic toxicities.

3.2.7.7.2 Lactating females are not eligible unless they have agreed not to breastfeed their infants.

3.2.7.7.3 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.7.7.4 Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation and for 2 months after the end of study treatment.

3.2.8 Regulatory Requirements

3.2.8.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.8.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

This is a single arm Phase 2 study to evaluate the use of CDX-011, an ADC directed against GPNMB. All subjects will receive CDX-011 at 1.9 mg/kg intravenously over 90 minutes every 21 days. Treatment will be discontinued if there is evidence of progressive disease or drug related toxicity that requires removal from therapy, as defined in Section 5.0. Therapy may otherwise continue for a maximum duration of 14 months or ~18 cycles, whichever occurs first. Radiographic imaging assessments of disease status obtained after Cycles 2, 4 and 6 will be compared to imaging done just prior to initiating therapy. For those patients remaining on protocol therapy, subsequent imaging studies for assessment of disease status will occur after every 3rd cycle.

Other therapy: Although not encouraged, subjects who achieve a partial response after Cycle 2 that is confirmed after Cycle 6 will be allowed to undergo resection of sites of disease or radiation and remain on protocol therapy. Therapy will be held during surgery and resumed when recovered from surgery but at least 2 weeks after surgery. CDX-011 therapy will be held during radiation and may be resumed upon completion of the radiation treatment course. If the patient has not recovered from surgery within 6 weeks the patient will go off protocol therapy. Surgery or radiation performed on any site of measurable disease before the end of the sixth cycle will render the patient inevaluable for disease control assessment and they will be removed from protocol therapy.

4.1.1 Concomitant Therapy

4.1.1.1 CYP3A4 inducers and inhibitors

The use of the following medications should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx or other frequently updated medical reference for additional information.

CYP3A4 substrates	Strong Inhibitors*	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil	atazanavir	aprepitant	amiodarone	armodafinil
amiodarone	boceprevir	atazanavir	ciprofloxacin	barbiturates
aprepitant	clarithromycin	cimetidine	doxycycline	bosentan
benzodiazepines	cobicistat	crizotinib	mifepristone	carbamazepine
bortezomib	conivaptan	cyclosporine	metronidazole	deferasirox
brentuximab	delavirdine	desipramine	nicardipine	efavirenz
budesonide	fosamprenavir	diltiazem	propofol	etravirine

calcium channel blockers cisapride citalopram/escitalopram glucocorticoids crizotinib cyclosporine cyclophosphamide dapsone dasatinib dihydroergotamine docetaxel doxorubicin ergotamine erlotinib esomeprazole estrogens etoposide fentanyl fosaprepitant gefitinib haloperidol HIV antiretrovirals HMG Co-A inhibitors ifosfamide imatinib irinotecan itraconazole ketoconazole lansoprazole lapatinib losartan lovastatin macrolide antibiotics medroxyprogesterone methadone midazolam modafinil monteleukast nefazodone nilotinib omeprazole ondansetron paclitaxel pazopanib quinidine sildenafil sirolimus sunitinib tacrolimus terfenadine telaprevir	indinavir itraconazole ketoconazole nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	erythromycin fluconazole fluvoxamine fosaprepitant grapefruit grapefruit juice imatinib norfloxacin tetracycline verapamil	quinidine sertraline tacrolimus	fosphenytoin glucocorticoids modafinil nafcillin nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone primidone rifabutin rifampin rifapentin ritonavir St. John's wort topiramate

tamoxifen temsirolimus teniposide trimethoprim vinca alkaloids zolpidem				

* Certain fruits and fruit juices (star fruit, Seville oranges, pomegranate) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.

4.1.1.2 The administration of P-gp inhibitors should be avoided while the patient is receiving protocol therapy due to risk of increased exposure to MMAE.

4.1.1.3 No other antineoplastic agents may be given while the patient is receiving protocol therapy.

4.1.1.4 Growth factors that support white cell number or function should only be administered for culture proven bacteremia, invasive fungal infection, or if there was a Grade 4 ANC of > 7 days duration in a previous cycle or a delay of > 14 days between cycles for neutropenia.

For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.2 Therapy Delivery Map – CDX-011

4.2.1 Therapy Delivery Map – All Cycles of CDX-011 Each cycle lasts 3 weeks (21 days). Treatment may continue for up to 14 months or 18 cycles, whichever occurs first. One cycle of treatment is described in this TDM. This TDM is on 2 pages. Use a copy of this page once for each cycle (please note cycle number below).	_____ Patient COG ID number _____ DOB

Begin CDX-011 therapy only when ANC ≥ 1000/µL; Platelets ≥ 75,000/µL (transfusion independent); Hemoglobin ≥ 8.0 g/dL (RBC transfusions allowed); Cr clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or a serum creatinine based on age/gender as per Section 4.2.3; Total bilirubin ≤ 1.5 x ULN for age; SGOT (AST) or SGPT (ALT) ≤ 110 U/L, and Serum albumin > 2 g/dL.

DRUG	ROUTE	DOSAGE	DAY	IMPORTANT NOTES
CDX-011 (glembatumumab vedotin) IND# 128248	IV over 90 minutes	1.9 mg/kg/dose	Day 1	Recalculate the dose prior to each infusion. Round dose to the nearest 1 mg. See Section 4.2.3 for complete details.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CDX-011 ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	____mg	a-l
		8*		(a-f)*
		21		g, h, i

Start the next cycle on Day 22 or as soon as starting criteria are met, whichever occurs later. Treatment should continue up to 14 months (or 18 cycles, whichever occurs first) in the absence of disease progression or unacceptable toxicity. If disease progression or unacceptable toxicity occurs, the patient will be taken off protocol therapy.
Note: Patients who receive surgery or radiation on any site of measurable disease prior to completion of the 6th cycle of therapy will be taken off protocol therapy.

* Cycle 1 only

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

All Cycles

4.2.2 Required Observations Prior to Cycle 1 and During All Cycles

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For Cycle 1 only, observations a-f can be performed up to 7 days before the start of therapy and imaging studies may be obtained within 2 weeks prior to the start of therapy.

a. Hx/PE/Wt /Ht. Prior to each cycle and on Day 8 of Cycle 1.

b. CBC/diff/platelets. Prior to each cycle and on Day 8 of Cycle 1.

c. Bilirubin & Creatinine. Prior to each cycle and on Day 8 of Cycle 1.

d. Electrolytes, BUN, Ca^{++}, PO_4, Mg^{++}. Prior to each cycle and on Day 8 of Cycle 1.

e. AST, ALT, albumin. Prior to each cycle and on Day 8 of Cycle 1.

f. Neurologic evaluation. Prior to each cycle and on Day 8 of Cycle 1. Assess for NCI CTCAE > Grade 2 neuropathy.

g. CT chest. Prior to Cycle 1 and following Cycles 2, 4, 6 and every 3rd cycle thereafter.

h. Tumor disease evaluation. Prior to Cycle 1 and following Cycles 2, 4, 6, and every 3rd cycle thereafter. Evaluations should include CT or MRI of all lesions meeting eligibility criteria. Use the same imaging modality for all disease evaluations. Patients who had a RECIST response (CR or PR) at Cycle 6 imaging evaluation are required to have a confirmatory scan following Cycle 8. For patients who undergo a surgical resection following Cycle 6, either a CT scan or MRI post-surgery to establish a new baseline is strongly recommended prior to re-initiating CDX-011 therapy. See Section 16.0 for details.

i. ^{18}FDG PET or Bone Scan. Prior to Cycle 1 and following Cycles 2, 4, 6, and every 3rd cycle thereafter. ^{18}FDG PET or bone scan is required at baseline. ^{18}FDG PET scan is an optional study, but if completed then a bone scan is not necessary. It is recommended to obtain MRI or CT scan of any lesion positive on bone or ^{18}FDG PET scan. Bone or ^{18}FDG PET scan is required to assess for new disease after Cycles 2, 4 and 6. Further bone scan or ^{18}FDG PET should be completed as clinically indicated at investigator discretion. For consistency, investigators are encouraged to utilize the same modality used at baseline to follow positive lesions that are identified with ^{18}FDG PET or bone scan. See Section 16.0 for details.

j. Pharmacokinetics. Cycle 1 only, Day 1 pre-dose, end of infusion, 1, 2, 4, 8 and 24 (+/- 4 hours) hours post infusion, 4 days (+/- 1 day) post infusion, 7 and 21 days post infusion. Required for the first 6 evaluable patients ≤ 14 years of age enrolled at COG sites. Optional for patients > 14 years of age and ≤ 21 years of age enrolled at COG sites. See Section 15.2 for details.

k. Tumor GPNMB expression (required). Submission of a formalin-fixed, paraffin-embedded (FFPE) sample of tumor tissue (block or 10 slides) from the most recent surgery (preferred) or from any previous biopsy or resection is mandatory within 4 weeks of enrollment. See Section 15.1 for details.

l. Pregnancy test. Prior to Cycle 1. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments (Include any held doses, or dose modifications)

All Cycles

All Cycles

4.2.3 Therapy During Cycle 1 and Subsequent Cycles

One cycle of CDX-011 treatment is described below. A cycle may be repeated every 21 days (3 weeks) if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, and detailed below.

CDX-011 (glembatumumab vedotin): Intravenously over 90 minutes
Day: 1
Dose: **1.9 mg/kg/dose.** Round doses to the nearest 1 mg.
Actual body weight will be recorded and used to calculate dose prior to each infusion. CDX-011 is to be diluted with D5W and administered using a 0.22 µm low protein binding in-line filter. Patient should receive post-infusion flush with appropriate volume of D5W administered at the same rate as CDX-011 infusion.

Note: Premedication is not required, but may be used as clinically indicated.

Monitoring during CDX-011 infusion:

- Vital signs should be assessed every 15 minutes for the first hour of the infusion, followed by every 30 minute assessment for the remainder of the infusion and post-infusion flush. More frequent assessment may be required based on the patient's clinical condition.

Criteria to start each cycle

- Patients must recover from toxicities at least possibly related to CDX-011 therapy to ≤ Grade 1 severity or baseline prior to beginning next cycle
- ANC ≥ 1000/µL
- Platelets ≥ 75,000/µL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or a serum creatinine based on age/gender as follows: [Threshold creatinine values were derived from the Schwartz formula for estimating GFR.][50]

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 110 U/L for the purposes of this study the ULN for SGPT is defined as 45 U/L.
- Serum albumin > 2 g/dL

The next cycle will start on Day 22 or as soon as starting criteria are met, whichever occurs later.
See Section 5.0 for Dose Modifications based on Toxicities.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Definition of Toxicities

NOTE: Any suspected or confirmed dose-limiting toxicity should be reported to the Study Chair within 24 hours of site knowledge of its occurrence.

5.1.1 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy.

Note: Dose limiting hematological and non-hematological toxicities are defined differently.

5.1.1.1 Hematological Dose Limiting Toxicity

- Grade 4 neutropenia for > 7 days
- Grade 4 febrile neutropenia
- Platelet count < 25,000/μL on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

5.1.1.2 Non-Hematological Dose-Limiting Toxicity

- Any Grade 3 or greater non-hematological toxicity, except for the following:
  - Grade 3 nausea and/or vomiting of < 3 days duration
  - Grade 3 or 4 fever < 5 days duration
  - Grade 3 infection < 5 days duration
  - Grade 3 rash < 5 days duration
  - Grade 3 pruritis < 5 days duration
  - Grade 3 fatigue < 5 days duration
  - Grade 3 non-hematologic laboratory abnormalities that resolve within 14 days to Grade 1, or to initial eligibility criteria, or to baseline (if the patient entered the study with existing toxicity). Note: for the purposes of this study the ULN for SGPT (ALT) is defined as 45 U/L.
  - Grade 3 infusion-related reactions < 24 hours duration (see Section 5.2.3)
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation.

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption will also be considered a DLT.

5.2 Dose Modifications for Adverse Events

The Study Chair must be notified of any use of myeloid growth factor for hematologic toxicity and of any other dosage modification described below.

Please note: Only one dose reduction to 1.3 mg/kg CDX-011 will be made prior to removal from protocol therapy for unacceptable toxicity.

5.2.1 Dose Modifications for Hematological Toxicity

Hematologic Toxicity	Action
Dose-limiting thrombocytopenia (platelets ≤ 25,000/μL on 2 separate days, or requiring a platelet transfusion on 2 separate days within a 7 day period)	• Patients should receive subsequent cycles at a reduced dose of CDX-011. Patients should have platelets ≥ 50,000/μL to start the subsequent cycle. If the prior dose of CDX-011 was 1.9 mg/kg, subsequent treatment will be with 1.3 mg/kg. • Patients who experience dose-limiting thrombocytopenia after dose reduction or dose-limiting neutropenia after addition of myeloid growth factor and one dose reduction must be removed from protocol therapy.
Grade 4 neutropenia that does not resolve to an ANC of ≥ 500/μL within 7 days after the next scheduled dose of CDX-011	• Patients with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support. Each subsequent cycle of CDX-011, after the first, should begin no sooner than Day 22 of the preceding cycle, and should not begin unless the ANC is ≥ 1000/μL. • Myeloid growth factor administration should begin on Day 2 of subsequent cycles and should continue until the post-nadir absolute neutrophil count is ≥ 2,000/μL. The administration of myeloid growth factor to the patient should cease at least 24 hours prior to starting the next cycle of CDX-011. • If dose-limiting neutropenia recurs after a myeloid growth factor is added, then the patient should be given a reduced dose of CDX-011 for subsequent cycles. If the prior dose of CDX-011 was 1.9 mg/kg, subsequent treatment will be with 1.3 mg/kg. If dose-limiting neutropenia recurs in a patient that has received a dose reduction but has not received myeloid growth factor, then myeloid growth factor should be administered or the patient should be removed from protocol therapy.

5.2.1.1 Patients who have a dose-limiting hematological toxicity that does not resolve to baseline within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

5.2.2 Dose Modifications for Non-Hematological Toxicity

Non-Hematologic Toxicity	**Action**
Any dose-limiting non-hematological toxicity (as defined in Section 5.1)	• Continue on protocol therapy upon meeting eligibility lab requirements but should receive subsequent cycles at a reduced dose of CDX-011. If the prior dose of CDX-011 was 1.9 mg/kg, subsequent treatment will be with 1.3 mg/kg. • If the same non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy. • Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

5.2.3 Dose Modifications for Infusion-Related Reactions

Infusion-related reactions (IRR), including anaphylaxis, were uncommon in adult studies with CDX-011. Infusion interruption for IRR treatment generally led to the successful completion of the dose and continued treatment with CDX-011 with or without IRR prophylaxis, according to the clinical judgment of the investigator. Although the experience with IRRs related to CDX-011 is limited, in part due to the low incidence observed to date, data support CDX-011 administration by appropriately trained personnel without the need for routine prophylaxis.

If IRR symptoms develop, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution (see below). Premedication with diphenhydramine should be administered for subsequent infusions in patients who have experienced a prior IRR. Dosing of diphenhydramine can be according to institutional standards, or 1 mg/kg PO or IV (maximum of 50 mg). If anaphylaxis occurs, CDX-011 should be immediately and permanently discontinued and appropriate medical management instituted.

5.2.3.1 Suggested dose modification for infusion-related reactions to CDX-011

If an infusion related reaction occurs, vital signs should be monitored every 5 minutes during infusion until patient is stable. After infusion is complete, vital signs should be monitored per institutional infusion standard. Therapy modifications for patients who

develop infusion-related reactions to CDX-011 should be:

Grade	Action

Grade 1
Transient flushing or rash, drug fever < 38°C (< 100.4°F)
or
Grade 2
Rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C (≥ 100.4°F)
	For first reaction:
	• Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity).
	• Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) IV should be used.
	• Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered.
	• **The rate of CDX-011 administration should be administered at half of the previously administered rate.**
	For all subsequent doses:
	• Utilize diphenhydramine with or without acetaminophen as pre-treatment. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines.
	• Dosing should be administered over the shortest period that was well tolerated.
	• If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments:
	  • Take the measures outlined above
	  • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10 mg) IV or equivalent to medications above prior to infusion.

Grade 3 Symptomatic bronchospasm with or without urticaria, allergy-related edema/ angioedema, hypotension	• Stop infusion immediately • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Hospital admission should be considered. • CDX-011 should not be resumed for that cycle. • Subsequent cycles of CDX-011 may be considered at physicians' discretion. • All subsequent infusions should be given with the following dose modifications: 1. Premedication with diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), and

Grade	Action
	dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. 2. The infusion should be administered at 50% of the previous infusion rate.
Grade 4 Anaphylaxis	• Stop infusion immediately • Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. • Protocol therapy should be discontinued.

5.2.4 Dose Modifications for Peripheral Neuropathy

Peripheral neuropathy is an effect of cumulative exposure to CDX-011. In adult studies, the first onset of any grade peripheral neuropathy increased with increasing numbers of cycles. Dose delay and reduction appeared to mitigate worsening of neuropathy.

PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

Peripheral Neuropathy	Action
Grade 2-3 neuropathy	• Treatment should be delayed until neuropathy improves to Grade 1 or baseline. The dose of CDX-011 in subsequent cycles should be reduced. If the original dose assignment of CDX-011 was 1.9 mg/kg, subsequent treatment will be with 1.3 mg/kg. • If Grade 2 or 3 neuropathy recurs after dose reduction as described above, patients will be taken off protocol therapy, and CDX-011 will be discontinued. Patients who experience a delay in therapy > 14 days due to peripheral neuropathy will be taken off protocol therapy, and CDX-011 will be discontinued.
Grade 4 neuropathy	• CDX-011 should be discontinued.

Note: All dose modifications should be based on the highest grade toxicity in the preceding cycle.

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

5.2.5 Dose Modifications for Dermatologic / Rash

A variety of rashes have been demonstrated with the use of CDX-011 including pruritus, dry skin, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, erythema and skin discoloration. At the current study dose 6% of breast cancer patients and 30% of the melanoma patients experienced Grade 3 dermatologic toxicity. Dermatologic toxicities were increased in higher or more frequent dosing schedules. These toxicities included fatal toxic epidermal necrolysis; Grade 4 cases of rashes and palmar-plantar erythrodysaesthesia syndrome; and Grade 3 cases of rash, pruritus, blisters, dermatomyositis, palmar-plantar erythrodysaesthesia syndrome, skin breakdown to perianal area, desquamation and hives. In addition, a serious adverse event of Grade 2 erythema multiforme was reported in a patient receiving a higher dose level.

Clinicians should be aware of the potential for patients to develop severe rashes and should examine skin at every visit. Signs of Steven Johnson's syndrome/toxic epidermal necrolysis may include a prodrome fever and influenza like symptoms followed by skin lesions. Skin lesions typically begin on the face and spread symmetrically to other body parts. The scalp, palms, and soles are usually spared. Skin lesion consist of coalescing erythematous macules with purpuric centers or diffuse erythema. Mucosal membranes are typically involved with oral mucosa with painful hemorrhagic erosions covered with a grayish-white membrane as well as stomatits and mucositis.

Dermatologic / Rash	**Action**
Grade 1 and Grade 2 toxicity of pruritus and/or dry skin	• Patients may use emollients and antihistamines for pruritus. • Less extensive rashes may be treated with topical corticosteroids and more extensive/severe rashes may be treated with systemic corticosteroids.
Grade 3 toxicity that does not resolve to Grade 1 or baseline within 5 days after the next scheduled dose of CDX-011	• Reduce subsequent doses as per Section 5.2.2.1.
Grade 4 toxicity	• CDX-011 should be discontinued

[redacted]

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy & Follow-up

STUDIES TO BE OBTAINED	End of Therapy
History	X
Physical exam with VS	X
Performance status	X
CBC, differential, platelets	X
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X
Creatinine, SGPT, bilirubin	X
Total protein/albumin	X
Tumor disease evaluation (see Section 16.0)	X

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data must be submitted in accordance with the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Unacceptable toxicity due to protocol therapy (see Section 5.0).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of planned therapy.
e) Physician determines it is in patient's best interest.
f) Development of a second malignancy.
g) Repeat eligibility studies (if required) are outside the parameters required for eligibility (see Section 3.2).
h) Surgery or radiation performed on any site of measurable disease before the end of the 6th cycle.
i) Failure to recover from surgery within 6 weeks.
j) Pregnancy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 **Off Study Criteria**

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 **Sample Size and Study Duration**

A review of enrollment on COG single-agent Phase 2 studies demonstrates that approximately 1.8 patients per month will potentially be eligible for AOST1521. A maximum of 29 outcome evaluable patients will be required for the evaluation of CDX-011 amongst patients without prior treatment with eribulin. Eribulin has not been used as a component of therapy for newly diagnosed patients in pediatric protocols and there has been only one COG study of that agent for patients with recurrent disease. As such, we expected no more than 15% of patients who are eligible for this study to have received eribulin as part of therapy prior to potential enrollment on this study. Providing for possible ineligible and inevaluable patients, the maximum enrollment will be 38 patients.

With these entry rates, the probability we will accrue at least 38 patients in 24 months is 80% and the corresponding probability for 30 months is in excess of 99%. The study will likely require 2 to 2.5 years to enroll sufficient patients. A maximum of 38 patients is anticipated.

9.2 **Study Design**

Feasibility Cohort: The first six (6) younger patients (< 18 years of age) who are evaluable for toxicity will be considered as the feasibility cohort. All such patients will be assigned to receive 1.9 mg/kg/dose. Enrollment to this cohort will not be segregated by prior treatment with eribulin. Study accrual will be suspended after the sixth patient is enrolled; enrollment of patients 18 years of age or older will continue regardless of the result in the feasibility cohort. If dose limiting toxicity (DLT) during the first cycle of therapy occurs in one or fewer evaluable patients then the trial accrual will proceed as outlined below. Patients who are enrolled in the toxicity cohort who receive the "feasible" dose of CDX-011 will be considered in the outcome evaluation rules presented below for the relevant patient stratum as it relates to prior eribulin exposure.

Patients will be enrolled in two stages. In the first stage, 19 disease control and RECIST response evaluable patients will be enrolled. Each patient will be evaluated for both outcome measures: (1) disease control success; and (2) RECIST response (CR or PR *v.* not CR or PR). The decision rule for the two stage study design is summarized as:

Stage	Number of Patients Enrolled in Stage	Cumulative Response Results	Decision
I	19	4 or fewer disease control successes	Terminate the trial with the conclusion that Glembatumumab

		and 1 or fewer RECIST responders	Vedotin is not associated with sufficient activity for further single agent investigation
		5 or more disease control success or 2 or more RECIST responders	Continue to stage II
II	10	8 or fewer disease control successes and 4 or fewer RECIST responders	Terminate the trial with the conclusion that Glembatumumab Vedotin is not associated with sufficient activity for further single agent investigation
		9 or more disease control successes or 5 or more RECIST responders	Terminate the trial with the conclusion that Glembatumumab Vedotin is associated with sufficient activity for further single agent investigation

Design Characteristics: Each patient enrolled will be evaluated for: (1) complete or partial response as defined by the RECIST criteria where the first evaluation of CR or PR is made at or before the end of the sixth cycle of study therapy (denoted as R below); or (2) stable disease after four months of therapy or at the end of the sixth cycle, whichever occurs first (denoted as S below). We will not be interested in promoting the agent for further investigation if the probability of response in any particular individual is less than or equal to 0.05 (P(R)≤0.05) and the probability of remaining analytic event free in any particular individual is less than or equal to 0.20 (P(S)≤0.20). We will be interested in promoting the agent for further investigation if the probability of response in any particular individual is at least 0.22 (P(R)≥0.22) **or** the probability of remaining analytic event free in any particular individual is at least 0.42 (P(S)≥0.42).

For the calculations below, it is assumed $\Pr(S \mid R) = 0.90$.

The statistical characteristics of this design are:

Probability of four month disease control	Probability of RECIST response	Probability of Stopping After Stage 1 (and concluding the drug is ineffective)	Probability of Concluding the Drug is Ineffective at the Conclusion of the Trial	Probability of Concluding the Drug is Effective at the Conclusion of the Trial
0.20	0.05	0.56	0.89	0.11
0.42	0.22	0.014	0.05	0.95
0.42	0.05	0.044	0.096	0.904
0.20	0.22	0.056	0.21	0.79

Prior Treatment with Eribulin: As noted in Section 9.1, we expect no more than 15% of patients will have been treated with eribulin prior to enrollment on AOST1521. Patients will be evaluated for S and R as described above. Enrollment to this stratum will be terminated when we can determine there are sufficient patients to fully evaluate the efficacy of CDX-011 in the stratum of patients without prior eribulin therapy. If 19 patients with prior eribulin therapy are enrolled, the staged design described above for patients without prior eribulin therapy will be applied to this stratum.

9.3 Methods of Analysis for Pharmacokinetics (Aim 1.2.2)

Data from all patients who provide samples for pharmacokinetic analysis will be aggregated. The sample mean and variance of the AUC, clearance and half-life will be calculated. No formal statistical testing will be done.

Pharmacokinetic studies are mandatory for the first 6 evaluable patients 14 years of age or less who are enrolled at an institution which is a member of COG. Consent for pharmacokinetic studies for any patient greater than 14 years of age and less than or equal to 21 years of age who is enrolled at a COG member institution is optional. PK sampling will not be sought for patients who are older than 21 years of age at the time of enrollment.

9.4 Evaluability for Disease Control and Response

Which Patients will be Considered Evaluable for RECIST Response:

Any eligible patient who receives at least one dose of CDX-011 will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy during the response evaluation period after the patient is considered as having a partial or complete response but prior to confirmation of this status by tumor imaging and before progressive disease is noted, the individual will be considered inevaluable for the response endpoint. Further, patients who stop CDX-011 after the 1st evaluation because of toxicities or death will be considered evaluable for the response evaluation and will be counted as non-responders for the response endpoint.

Which Patients Will Be Considered Evaluable for Disease Control Success:

Any eligible patient who receives at least one dose of CDX-011 will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy during the first four months of therapy or first six cycles of therapy, whichever occurs first, is considered as having a partial or complete response but prior to confirmation of this status by tumor imaging and before progressive disease is noted, the individual will be considered inevaluable for the disease control success endpoint.

Which Patients Will be Considered a Disease Control Success:

Any patient who is evaluated free of all detectable disease (complete response) or is considered as having a partial response or is considered as having stable disease (‘at least stable disease’) after four months of therapy or at the end of the sixth cycle, whichever occurs first.

Which Patients Will be Considered Not a Disease Control Success:

Any evaluable patient who does not meet the criteria for disease control success (complete response, partial response or stable disease) will be considered to not have experienced disease control success.

In particular, any patient who dies because of treatment-related toxicity during the first six cycles of therapy and within the first four months since starting treatment will be considered not to have experienced disease control success. Also, any patient who is eligible, receives one dose of CDX-011 and is lost to follow-up at (for example) the end of cycle 2 will be considered not a disease control success (complete response, partial response or stable disease).

Patients who are not evaluable for both disease control and response evaluation may be replaced for the purposes of the statistical rule.

9.5 Evaluability for Toxicity

Tolerability of CDX-011 - An eligible patient will be considered for toxicity monitoring if one of the following occurs: (1) complete one cycle of CDX-011 prior to receiving non-protocol anticancer therapy; (2) die on protocol therapy for a reason considered possibly, probably or likely related to CDX-011; or (3) are removed from protocol therapy because of an adverse experience possibly, probably or likely related to CDX-011. A toxicity-evaluable patient will be considered in the analysis during the interval from study enrollment until the termination of protocol therapy. A toxicity-evaluable patient will be considered to have experienced an excessive toxicity event if: (1) the patient dies on protocol therapy for a reason considered possibly, probably or likely related to; or (2) experiences a dose-limiting toxicity (DLT). DLTs will be as defined in Section 5.1.1 of the protocol:

The analytic unit for monitoring for excessive toxicity will be the patient-cycle: Each cycle where the patient receives CDX-011 and does not receive non-protocol anticancer therapy will be considered in the analysis. If there is overwhelming evidence that the dose selected for this trial has a per-cycle-DLT probability of more than 30%, we will identify the regimen to the COG DSMC, Bone Tumor Committee leadership and CTEP as associated with a toxicity profile that may require modification of the regimen. We will use a Bayesian rule to monitor for excessive toxicity. We will assume a beta prior to distribution with α=0.6 and β=1.4. If this posterior probability of the chance of DLT is at least 30% exceeds 80%, we will identify the regimen to the COG DSMC, Bone Tumor leadership and CTEP as associated with a toxicity profile that may require modification of the regimen.

9.6 Estimation of Disease Control and RECIST Response Rates

P(R) and P(S) for each cohort defined by prior eribulin exposure will be estimated using the maximum likelihood estimates, *viz.*,

$$P(R) \doteq \hat{p}_R = \frac{Number\ of\ \ Patients\ Considered\ as\ PR\ or\ CR}{Number\ of\ \ Evaluable\ Patients\ in\ Cohort};$$

$$P(S) \doteq \hat{p}_S = \frac{Number\ of\ \ Patients\ With\ Disease\ Control\ at\ 4\ Months}{Number\ of\ \ Evaluable\ Patients\ in\ Cohort}$$

Confidence intervals will be constructed using the approximate normal distribution of each of the estimates and their asymptotic variances:

$$V\left(\hat{p}_R\right) \doteq \frac{\hat{p}_R\left(1-\hat{p}_R\right)}{Number\ of\ \ Evaluable\ Patients\ in\ Cohort};$$

$$V\left(\hat{p}_S\right) \doteq \frac{\hat{p}_S\left(1-\hat{p}_S\right)}{Number\ of\ \ Evaluable\ Patients\ in\ Cohort}$$

9.7 Statistical Considerations for Secondary Aim 1.2.3

9.7.1 *To determine the relationship of GPNMB expression by IHC to response in tumor specimens from patients:* Submission of archival tissue will be required for this study. The primary cohort to address this aim will be the patients who were not previously treated with eribulin. The GPNMB expression IHC result will be coded as an integer between 0 and 3 with 0 being no GPNMB expression and 3 indicating strong GPNMB expression. The outcome measure will be DC success (Yes *v.* No). Logistic regression using the categorical IHC result will be fitted to the data. The fitted coefficients from the logistic regression, and the p-value for the test of the hypothesis of no relationship between IHC result and probability of DC success will be used to characterize this secondary analysis. Trend will also be assessed using the actual IHC numerical value.

9.8 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

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	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	6	0	0	**8**
White	9	17	1	3	**30**
More Than One Race	0	0	0	0	**0**
Total	**11**	**23**	**1**	**3**	**38**

This distribution was derived from ADVL0821, ADVL0921, ADVL1221.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria for Patients with Solid Tumors

For the purposes of this study, patients should be evaluated for response following Cycles 2, 4 and 6 and following every 3rd cycle thereafter. Patients who have a RECIST response (CR or PR) at Cycle 6 will have confirmatory imaging after Cycle 8.

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).[51] 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.

10.2.1 Disease Parameters

10.2.1.1 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 by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

10.2.1.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm 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.

10.2.1.4 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.

10.2.1.5 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.

10.2.2 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.

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

10.2.2.2 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.

10.2.2.3 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 or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, 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.

10.2.2.4 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.

10.2.2.5 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.

10.2.2.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

10.2.3 Response Criteria

10.2.3.1 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.

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. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.2.3.2 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 short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): 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).

10.2.3.3 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 (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	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.
**Only for non-randomized trials with response as primary endpoint.
***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 (ie, 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

10.2.4 Duration of Response

10.2.4.1 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.

10.2.4.2 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.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting table assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
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 a serious adverse drug experience 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.

11.3 Specific Examples for Expedited Reporting

11.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

11.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it

occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered serious AEs.

11.3.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- 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.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.3.4 Secondary Malignancy

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

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

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

11.3.5 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 reporting via CDUS unless otherwise specified.

11.3.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.6.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions***" SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.3.6.2 Pregnancy Loss (Fetal Death)

Pregnancy loss is defined in CTCAE as "*Death in utero.*" Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.3.6.3 Death Neonatal

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*" should be reported expeditiously, as **Grade 4 "*Death neonatal*" under the "*General disorders and administration*" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.

c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.4.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.4.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5 Exceptions to Expedited Reporting

11.5.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.5.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting table for this protocol.

11.6 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.7 General Instructions for Expedited Reporting via CTEP-AERS

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 website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# 310-640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.8 **Reporting Table for 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]

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) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
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 CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

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. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs 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 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.9 **Protocol Specific Additional Instructions and Reporting Exceptions**

- **Grades 1- 4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**
- **Grades 1-2 peripheral neuropathy do not require expedited reporting.**

11.10 **Routine Reporting of Adverse Events**

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher non-hematologic and Grade 4 and higher hematologic Adverse Events

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 **CDUS**

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 **Data and Safety Monitoring Committee**

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (eg, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 **CRADA/CTA**

NCI/DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and

Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

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.

13.0 SURGICAL GUIDELINES

See COG Surgical Guidelines for osteosarcoma at:
https://members.childrensoncologygroup.org/_files/Disc/surgery/handbooks/OsteoBoneHandbook.pdf

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

All patients enrolling on this protocol require institutional histological confirmation of osteosarcoma at the time of original diagnosis or relapse. Patients are required to submit archival tumor samples (collected at original diagnosis or at relapse or at any subsequent resections or biopsies) for immunohistochemical analysis.

Please note: At enrollment, all patients must have adequate tumor specimen available for submission as detailed in Section 3.2.3.

Autopsy
In the event of patient death on AOST1521, a complete unrestricted postmortem examination is strongly encouraged. For patients enrolled on AOST06B1at COG sites, tissue submission at

autopsy is requested. (See AOST06B1 protocol.)

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Tumor GPNMB Expression (mandatory participation)

15.1.1 Required specimen

Submission of a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from the most recent surgery (preferred) or from any previous biopsy or resection is **required**. Alternatively, if a FFPE tumor block cannot be provided, then 10 unstained, positively-charged slides must be submitted. Each slide should be cut at 4-5 μm thickness. If multiple blocks from prior surgery/biopsy sites are available (including primary tumor tissue), sites are encouraged to submit one block from each, as this will allow investigation GPNMB expression as it varies between primary, advanced and metastatic lesions, as well as over time. The tumor material must be sent within 4 weeks of patient enrollment. All tissue blocks will be repatriated to the originating investigative site at the end of the study. For expedited repatriation of tissue blocks (not slides) due to urgent clinical need, contact Mosaic Laboratories.

15.1.2 Sample Collection and Processing

FFPE samples and slides can be stored indefinitely at room temperature away from direct sunlight prior to shipment. Tissue samples for GPNMB testing should not be frozen and thawed prior to embedding in paraffin.

Please note: Pathology specimens must be fixed with 10% formalin. Other fixative agents are not acceptable.

15.1.3 Sample Labeling and Shipping

All tumor material must be labeled with the patient's COG patient ID number, specimen type, block number and collection date. Please ensure the local pathology accession number (block number) is visible and legible on the paraffin block. If not legible, provide documentation verifying block number on the Specimen Submission Form. Please upload a copy of the pathology report in RAVE and include a printed copy with the shipment. Please complete the study specific Tumor GPNMB Specimen Submission Form in RAVE and provide a printed copy with each shipment. If multiple blocks or slide sets are submitted, each tissue specimen sent should have a separate form to identify the tissue sent. Samples received without a pathology report are considered incomplete.

- Circle or underline the pathology accession number and block ID on the pathology report for the pathology specimens submitted. 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.

The samples are to be shipped at room temperature to the following address:

Mosaic Laboratories
Attn: Clinical Trials
12 Spectrum Pointe Drive

Lake Forest, CA 92630

Please contact Mosaic Laboratories and provide the Tumor GPNMB Specimen Submittal Form by fax or email **before** shipping specimens:
Fax: (949) 340-7330
E-mail: clinicaltrials@mosaiclabs.com

On the day of shipment, send notification with tracking information to:
Fax: (949) 340-7330
E-mail: clinicaltrials@mosaiclabs.com

Please note: Tumor samples should be shipped on Monday through Friday using overnight shipping. Tumor Tissue may be shipped for Saturday Delivery. The laboratory does not accept deliveries on the following US holidays (or the day prior to these holidays): New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, and Christmas Day. 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. 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.

For lab questions, call: (949) 340-7598.

15.1.4 Methodology
Immunohistochemistry for GPNMB expression in osteosarcoma tissue will be performed by Celldex Therapeutics (Mosaic Laboratories, Lake Forest, CA).

15.2 Pharmacokinetics

Participation in the PK studies is limited to COG member institutions. Serial blood samples for the assessment of CDX-011, CR011 antibody and MMAE are **required** for the first 6 evaluable patients ≤ 14 years of age enrolled at a COG member site. Serial blood samples for the assessment of CDX-011, CR011 antibody and MMAE are **optional** for patients > 14 years of age and ≤ 21 years of age enrolled at a COG member site.

15.2.1 Timing of pharmacokinetic sampling
Blood samples will be obtained in Cycle 1 on Days 1, 4 (+/- 1 day), 7 and 21 at the following 10 time points related to CDX-011 dosing:

- Time 0 (pre-dose)
- End of infusion
- 1 hour post infusion
- 2 hours post infusion
- 4 hours post infusion
- 8 hours post infusion
- 24 hours (+/- 4 hours) post infusion
- 4 days (+/- 1 day) post infusion
- 7 days post infusion
- 21 days post infusion

15.2.2 Sample Collection and Processing

At each specified time point, fill one appropriately labeled (water and freezer proof ink) 5.0 mL red-top Vacutainer® tube, containing no anti-coagulant until the vacuum is exhausted and blood flow ceases. Gently invert the filled tube 8 times and allow to clot for 15 to 30 minutes at room temperature.

Centrifuge at 3000 rpm for 15 minutes at room temperature (if you have a temperature controlled centrifuge set to 20^0C).

Prepare four 2-mL cryovials per subject per time point. Each tube should have a freezer-safe label with:

- AOST1521
- COG patient ID number
- Study day
- Actual time of collection
- Sampling date

Using a pipette, remove serum from the top of the tube without disturbing the blood cells and transfer an ***equal volume*** (ideally 0.5-1 mL each) into each of the four labeled 2 mL cryovials**.**

Note: If there is an inadequate amount of serum for 0.5-1 mL per cryovial then split the available serum volume equally into all cryovials.

Immediately place the 2 mL cryovials containing the serum sample in a -20^0C (or colder) freezer. All tubes should be stored in an upright position.

The serum sample must be frozen within 2 hours of blood collection.

Following the plasma harvest, the remaining buffy coat and red blood cell layers should be discarded as biological specimen.

15.2.3 Sample Labeling and Shipping

Each tube should have a freezer-safe label with the details listed in Section 15.2.2 above. Each shipment should be prepared in accordance with IATA regulations.

If feasible, specimens should be collected at the clinical site and shipped in a batch to the lab. Specimens must be shipped in accordance with rules and laws governing the shipment of human diagnostic specimens.

No shipments should be made within 3 days of a holiday.

All tubes are to be shipped frozen in appropriately insulated containers with enough dry ice to last 3 days. The tubes should be shipped on the first Monday, Tuesday, or Wednesday following the last scheduled sample collection by **overnight delivery** such that they reach the lab before or by Thursday of that week. The PK transmittal form must be completed in RAVE and a printed copy submitted with the samples to the following address:

Attention: Jodi Bonfiglio
Celldex Therapeutics, Inc.
119 Fourth Avenue
Needham, MA 02494

Email lab@celldex.com at least 24 hours prior to shipment.

On the day of shipment: Email a copy of the study-specific paper PK transmittal form and the tracking number to lab@celldex.com and copy the **AOST1521 COG Study Research Coordinator** on the email.

For lab questions, Jodi Bonfiglio can be contacted as follows:
Phone: (781) 433-3127
Fax: (781) 433-0262
E-mail: jbonfiglio@celldex.com

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

16.1 Required and Recommended Osteosarcoma Imaging

Site	Anatomic Imaging	Functional Imaging	Timing
Primary tumor and bone metastases	AP and lateral radiographs		At presentation, following Cycles 2, 4, 6, and following every third cycle thereafter.
Primary tumor and bone metastases	CT or MRI with gadolinium		At presentation, following Cycles 2, 4, 6*, and following every third cycle thereafter.
Chest	CT		At presentation, following Cycles 2, 4, 6, and following every third cycle thereafter.
Whole body		^{18}FDG PET **or** MDP bone scintigraphy (recommended, not required)	Recommended at presentation. If a bone scan or ^{18}FDG PET is positive, it should be repeated following Cycles 2, 4, 6 and following every third cycle thereafter.

*For patients who undergo a surgical resection following Cycle 6, either a CT scan or MRI post-surgery to establish a new baseline is strongly recommended before re-initiating CDX-011 therapy.

NOTE: patients who have a RECIST response (CR or PR) at Cycle 6 will have confirmatory imaging after Cycle 8.

16.2 Technical Guidelines for Imaging Studies

16.2.1 CT and MRI guidelines are available on the COG Member site at: http://members.childrensoncologygroup.org/_files/reference/RefMaterial/DiagnosticImagingGuidelines_MRI&CT.pdf

16.2.2 X-ray

AP and lateral radiographs of primary tumor and bone metastases

16.2.3 Bone Scan (Recommended)

MDP bone scintigraphy

- Whole body bone scintigraphy should be performed and include planar images of the skeleton, including anterior and posterior views of the axial skeleton. Anterior and/or posterior views should be obtained of the appendicular skeleton.
- Delayed (skeletal phase) images should be performed in all cases with flow and blood pool images as per local custom and clinical need.
- Dose Administration: Dose administered should be according to standard weight-based protocols. Injection site should be away from lesion extremity or contralateral extremity if flow imaging is to be performed. Three-phase imaging is not required unless warranted by symptoms for a focal lesion to assess hyperemia.
- Imaging Parameters: Whole body delayed imaging is acquired 2-3 hours after injection of the radiopharmaceutical. Spot views should be acquired of specific sites of symptoms or of any sites of abnormality as warranted by the whole body views.
- Single-photon emission computed tomography (SPECT) is recommended, but not required, particularly in cases with suspicion of lung metastases.
- SPECT Imaging: SPECT should be performed of the lesion site. SPECT imaging should be performed as recommended by the camera manufacturer. Typical acquisition and processing parameters are 360° circular orbit, 60–120 stops, 64 ´ 64 ´ 16 or greater matrix, and 10–40 s/stop. An equivalent total number of counts should be acquired if continuous acquisition is used.
- Special Consideration: Imaging of pelvis can be difficult due to overlying bladder activity. To lessen this problem, repeat imaging can be performed immediately after patient voiding. Bladder catheterization may be used, but should be reserved for patients in whom visualization of the pelvis is essential. For SPECT acquisition of the pelvis: Single or multiple rapid (5-10 min/acquisition) SPECT acquisition(s) are preferred to avoid artifacts caused by changing activity in the bladder. Bladder artifacts are exaggerated in the plane in which the SPECT acquisition begins and ends. Beginning SPECT acquisition with the camera heads in the left and right lateral positions (for dual-head camera) or posterior position (for single-head camera) will help reduce bladder filling artifact.

16.2.4 [^{18}F]–Fluorodeoxyglucose Positron Emission Tomography (FDG PET) Imaging (Recommended)

FDG PET imaging is optional, but is encouraged for all patients. The primary lesion must be ≥ 1 cm on baseline anatomic imaging in order for a FDG PET scan to be performed. If done, FDG PET imaging should be performed prior to the start of therapy and following Cycle 2, Cycle 4, Cycle 6 and following every 3rd cycle thereafter.

Patient Guidelines

The patient should fast for at least 4 hours prior to injection of FDG. FDG PET imaging may follow a MUGA study on the same day, or FDG PET imaging may be performed on the day preceding this study. Plasma glucose should be checked and, if the patient is hyperglycemic (plasma glucose > 250 mg/dL), appropriate treatment with small doses of insulin may be given to bring the plasma glucose into the normal range prior to FDG PET imaging. However, insulin administration may result in excessive muscle uptake of FDG and consequent tumor non-visualization. If possible, the study should be postponed until the plasma glucose is under better control.

Good hydration is required, as the primary route of FDG excretion is renal. The patient should drink water or receive intravenous fluids (not containing dextrose) after FDG injection to promote urinary excretion of the radioactive substrate. After injection, the patient must be kept in a resting state for 45-60 minutes prior to imaging. The patient should empty the bladder immediately prior to imaging.

Imaging Technique

The technique will vary by local institutional guidelines. In general, FDG is administered intravenously at a dose of 0.125-0.200 mCi/kg or by algorithms that adjust the dose by body surface area, with a minimum total dose of 2.0 mCi and maximum total dose of 20.0 mCi.

The body should be imaged from the top of the ears to the bottom of the feet. If there is suspicion of involvement of the skull or skull contents, the volume that is imaged should be expanded.

Imaging with a dedicated positron emission tomograph/computed tomography (PET/CT) camera is standard.

The length of time needed to perform head to toe CT will depend on the patient's height but will be approximately 45 seconds. Contiguous axial images should be obtained at 5 mm thickness using 90 mA and 120 Kv and adjusted for local institutional protocol. No oral or IV contrast is required but either or both are permissible and may be of benefit in cases where intraabdominal or pelvic pathology is a specific concern. With regard to patient positioning, the arms can be placed in a comfortable position at the patient's sides as long as they fit into the field of view. If the patient is large it may be necessary to lay the arms across the abdomen and hold in position with a stabilizing device.

Study Processing

The FDG PET study is processed for display by an iterative reconstruction algorithm. FDG activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake values (SUV). Uptake time, glucose levels, and partial volume effects influence both methods. The SUV

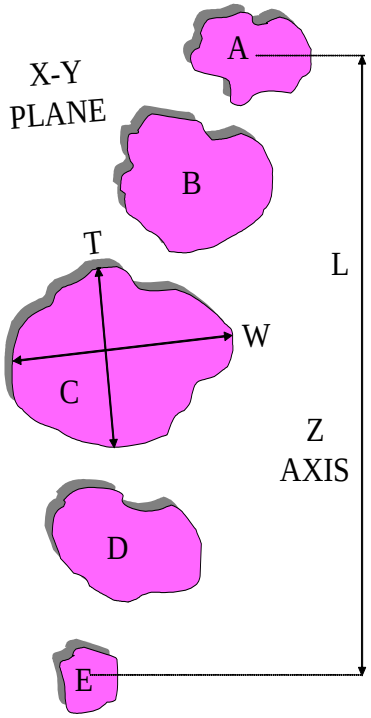
method is also dependent on body weight, and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. SUVs should be calculated for lesions known to be 1.2 cm or larger in diameter. Smaller lesions may have underestimated SUVs due to partial volume averaging effects at typical scanner resolutions (0.6-1.2 cm).

To calculate the SUV, a region of interest (ROI) should be carefully drawn around as much of the area of elevated FDG uptake as can be done. The SUV should be calculated as SUV_{BSA} = ROI activity concentration (nCi/cc) x BSA / injected activity (nCi). SUV_{MAX} is obtained by determining the activity of the pixel with the highest FDG uptake.

The BSA is calculated from body mass (kg) and height (cm) using an appropriate algorithm. The SUV_{BSA} for each measured lesion should be recorded and the technique for assessing SUV_{BSA} should be consistent on follow-up studies.

RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")

	Diameter, 2R	Product, $(2R)^2$	Volume, $4/3\pi R^3$
Response	**Decrease**	**Decrease**	**Decrease**
	30%	50%	65%
	50%	75%	87%
Disease Progression	**Increase**	**Increase**	**Increase**
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor

W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area

Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor *plus* one *slice* thickness), or [b] the product of ([slice thickness + gap] and the number of slices showing the tumor) *minus* one *gap* distance

- WHO criteria: TxW is used
- RECIST: the larger of the two (T & W) is used (W in this example)
- Elliptical model volume=0.5 LxWxT
- The same modality and measurement method used in the initial imaging should be used in follow ups

Target lesions at baseline must measure greater than 1 cm; if these target lesions decrease in size to below 1 cm, care should be taken in measuring and inadvertently progressing a patient due to minimal changes in measurement from a nadir value below 1 cm, which may be within measurement error. When multiple primary or metastatic masses are present, all masses will be described. However, up to 5 target masses should be measured, using the same method in subsequent follow ups.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR 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, 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 will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the AOST1521 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the COG link to expand, then select trial protocol AOST1521
- Click on the Site Registration Documents link

Requirements for AOST1521 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval 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)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AOST1521 (for subjects from 7 to 12 years of age)

A trial using a new drug, CDX-011, to treat osteosarcoma that has not responded to treatment or that has come back

1. We have been talking with you about your illness, osteosarcoma. Osteosarcoma is a type of cancer that grows in the cells that produce bones. After doing tests, we have found that you have this type of cancer and it has not gotten better with treatment or it has come back.

2. We are asking you to take part in a research study because you have osteosarcoma and it has not gotten better with treatment or it has come back. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat osteosarcoma that has come back. We will do this by giving a new drug to treat osteosarcoma. We do not know how well the new drug will work in children, teens and young adults. That is why we are doing this study.

3. Children who are part of this study will be given an experimental new drug called CDX-011. You will also have scans to see if the cancer is getting worse, staying the same or getting better. There is a possibility that you will also have surgery or radiation therapy (high energy x-rays to kill cancer cells) while you are part of this study. Surgery and radiation therapy are often used to treat osteosarcoma and they are not experimental.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is that you are able to get rid of the cancer. But we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” Being in this study may involve special risks, which your doctor will discuss with you. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are trying to learn about how children’s bodies handle the new drug CDX-011. If you are getting treatment at certain hospitals, we will take extra blood samples from you for research tests. These samples will be drawn through your central line if you have one.

   If you are getting treatment at a different hospital, we are asking your permission to collect additional blood. We are trying to learn how child and teenage bodies handle the new drug. These additional blood tests may help children, teens and adults who take this drug in the future. These blood tests will require additional blood draws, which will be drawn through your central line if you have one. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AOST1521
(for subjects from 13 to 17 years of age)

A trial using a new drug, CDX-011, to treat osteosarcoma that has not responded to treatment or that has come back

1. We have been talking with you about your illness, osteosarcoma. Osteosarcoma is a type of cancer that grows in the cells that produce bones. Recurrent means that the cancer has come back after treatment. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have recurrent osteosarcoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat osteosarcoma that has come back. We will do this by giving a new drug to treat recurrent osteosarcoma. We do not know how well the new drug will work in children, teens and young adults. That is why we are doing this study.

3. Children and teens and young adults who are part of this study will be given an experimental new drug called CDX-011. You will also have scans to see if the cancer is getting worse, staying the same or getting better. There is a possibility that you will also have surgery or radiation therapy (high energy x-rays) while you are part of this study. Surgery and radiation therapy are commonly used to treat osteosarcoma and they are not experimental.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that you are able to get rid of the cancer. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." Being in this study may involve special risks, which your doctor will discuss with you. Other things may happen to you that we don't yet know about.

6. You or your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Please talk this over with your parents. Together you can decide if you want to take part in the study or not. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are trying to learn about how children's bodies handle the new drug CDX-011. If you are getting treatment at certain hospitals, we will take extra blood samples from you for research tests. These samples will be drawn through your central line if you have one.

   If you are getting treatment at a different hospital, we are asking your permission to collect additional blood. We are trying to learn how child and teenage bodies handle the new drug. These additional blood tests may help children, teens and adults who receive this drug in the future. These blood tests will require additional blood draws, which will be drawn through your central line if you have one. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

APPENDIX III: POSSIBLE DRUG INTERACTIONS

The list below does not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Drugs that may interact with CDX-011 (glembatumumab vedotin)*

• **Antibiotics**
  ○ **Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin**
• **Antifungals**
  ○ **Itraconazole, ketoconazole, posaconazole, voriconazole)**
• **Arthritis medications**
  ○ **Leflunomide, tofacitinib**
• **Anti-rejection medications**
  ○ **Cyclosporine, sirolimus, tacrolimus**
• **Antiretrovirals and antivirals**
  ○ **Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir**
• **Anti-seizure medications**
  ○ **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone**
• **Heart medications**
  ○ **Nicardipine, verapamil**
• **Some chemotherapy (be sure to talk to your doctor about this)**
• **Many other drugs, including the following:**
  ○ **Aprepitant, bosentan, deferasirox, dexamethasone, lomitapide, natalizumab, nefazodone**

Food and supplements that may interact with CDX-011 (glembatumumab vedotin)**
• **Echinacea** • **St. John's Wort** • **Grapefruit, grapefruit juice, Seville oranges, star fruit**

**Sometimes these drugs are used with CDX-011 (glembatumumab vedotin) on purpose. Discuss all drugs with your doctor.*
***Supplements may come in many forms such as teas, drinks, juices, liquids, drops, capsules, pills, and dried herbs. All forms should be avoided.*

APPENDIX IV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **CDX-011**. 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.

These are the things that you as a healthcare provider need to know:

CDX-011 (glembatumumab vedotin) interacts with certain specific enzymes in your liver* and certain transport proteins that help move drugs in and out of cells**.

- *The enzyme in question is CYP3A4. CDX-011 (glembatumumab vedotin) is metabolized by CYP3A4. Patients must be closely monitored for adverse reaction if strong inhibitors or inducers are administered with CDX-011 (glembatumumab vedotin).
- **The protein in question is P-glycoprotein (P-gp). CDX-011 (glembatumumab vedotin) requires P-gp to move in and out of cells. Patients receiving P-gp inhibitors concomitantly with CDX-011 (glembatumumab vedotin) should be closely monitored for adverse reactions.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

CDX-011 (glembatumumab vedotin) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:
CDX-011 (glembatumumab vedotin) must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of CYP3A4 or transport protein P-gp".

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
  - Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug *CDX-011 (glembatumumab vedotin)***.** This clinical trial is sponsored by the NCI. *CDX-011 (glembatumumab vedotin)* may interact with drugs that are ***processed by your liver or use certain transport proteins in your body***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

CDX-011 (glembatumumab vedotin) interacts with a ***specific liver enzyme called CYP3A4 and transport protein P-gp*** and must be used very carefully with other medicines that interact with ***this enzyme or transporter***.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"strong inducers/inhibitors or substrates of CYP3A4 or P-gp transporter.***"
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

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