Protocol CDX011-04

A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, GPNMB Over-Expressing, Triple-Negative Breast Cancer (The "METRIC" Study)

Sponsored by: Celldex Therapeutics, Inc.

[redacted]

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

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1. STUDY PERSONNEL AND STUDY ADMINISTRATION

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

2. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADC	Antibody-Drug Conjugate
AE	Adverse Event
ALT (SGPT)	Serum Glutamic Pyruvate Transaminase (Alanine Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Serum Glutamic Oxaloacetic Transaminase (Aspartate Transaminase)
AUC	Area Under The Curve
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCTD	Division of Cancer Treatment and Diagnosis
DHHS	Department of Health and Human Services
DOR	Duration of Response
DPD	Dihydropyrimidine Dehydrogenase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Estrogen Receptor
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GPNMB	Glycoprotein NMB
HER2	Human Epidermal Growth Factor Receptor 2
HIPAA	Health Insurance Portability and Accountability Act
IC	Investigator's Choice
ICH	International Conference on Harmonization

Abbreviation	Definition
IDMC	Independent Data Monitoring Committee
IgG_2	Immunoglobulin G, Subclass 2
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
ITT	Intention to Treat
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
i.v.	Intravenous
Kg	Kilogram
LCMS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliters
MMAE	Monomethylauristatin E
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (of the United States)
NCIC	National Cancer Institute of Canada
NE	Inevaluable
NIH	National Institutes of Health
NR	Not Reported
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell

Abbreviation	Definition
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response or Progesterone Receptor
qw	Every week
q2/3w	Two of three weeks
q3w	Every three weeks
RBC	Erythrocyte Count
RECIST	Response Evaluation Criteria for Solid Tumors
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SD	Stable Disease
SOPs	Standard Operating Procedures
TdP	Torsades de Pointes
TNBC	“Triple Negative” Breast Cancer
ULN	Upper Limit of Normal
vc	Valine-Citrulline
WBC	Leukocytes

3. PROTOCOL SYNOPSIS

Protocol number:	CDX011-04
Title:	A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, GPNMB Over-Expressing, Triple-Negative Breast Cancer.
Investigational Treatment:	CDX-011 (Glembatumumab Vedotin; CR011-vcMMAE): a fully-human IgG_2 monoclonal antibody (CR011) against GPNMB coupled to MMAE via a protease-sensitive valine-citrulline peptide linker.
Control Comparator:	Capecitabine: an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine which is converted to 5-fluorouracil.
Indication:	Patients with metastatic, GPNMB over-expressing, triple-negative breast cancer, who have failed taxane therapy and who have received anthracycline therapy or for whom anthracycline therapy is not clinically indicated.
Number of Patients:	Approximately 300 patients will be enrolled (randomized 2:1 to CDX-011 or capecitabine).
Number of Study Centers:	Approximately 100-175 study centers will participate.
Objectives:	Primary: • To evaluate the anti-cancer activity of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer as measured by the duration of progression-free survival (PFS) Secondary: • To further assess the anti-cancer activity of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer, as assessed by the objective response rate (ORR), duration of response (DOR) and overall survival (OS) • To further characterize the safety of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer • To obtain pharmacokinetic parameters and to explore the relationships between patient-specific measures of exposure and safety and activity parameters Exploratory: • To assess whether treatment with CDX-011 is associated with improvement in quality of life and/or cancer-related pain as reflected by reduced analgesic use
Overview of study design:	This is a pivotal, open-label, prospectively controlled, randomized study of CDX-011 in patients with metastatic GPNMB-expressing triple-negative breast cancer. Eligible patients will be randomized (2:1) to receive CDX-011 or capecitabine. Enrollment will be stratified as follows: • 0-1 prior line of chemotherapy for advanced disease vs. 2 prior lines of chemotherapy for advanced disease. • Progression-free interval ≤ 6 months after receipt of taxane therapy vs. progression-free interval > 6 months after receipt of taxane therapy • Received anthracycline therapy previously vs. no prior anthracycline therapy Study treatment, and associated study visits at 3 week intervals, will continue until disease progression or intolerance. Tumor assessments will be performed at six week intervals for six months and nine week intervals thereafter, until disease progression.

	Upon discontinuation of study treatment, patients will be permitted to receive appropriate alternate anti-cancer therapies and will be followed for progression-free survival (if progression is not yet documented) and overall survival. The study analyses of PFS, ORR, and DOR will be based on tumor response assessments performed by an independent review committee according to RECIST 1.1 guidelines (Eisenhauer, Therasse et al. 2009) (**Appendix 3**). The investigator's assessment of tumor response (according to RECIST 1.1) will guide clinical management and eligibility for continuation of study treatment. An independent data monitoring committee (IDMC) will review cumulative data on an interim basis. The interim data reviews may include but are not limited to summaries of adverse events, laboratory values and vital signs. The IDMC will conduct reviews approximately every 6 months, or as frequently as deemed necessary by the IDMC, starting from the first randomized patient. If a safety concern is identified, the IDMC may recommend modifying, halting or permanently stopping the trial at any time.
Study Treatment Dosing and Administration	CDX-011 will be administered on Day 1 of repeated 21 day cycles. The starting CDX-011 dose is 1.88 mg/kg, given as a 90-minute intravenous infusion using a 0.22 µm in-line filter. Treatment will continue until progression or intolerance. Capecitabine will be orally administered on Days 1-14 of repeated 21 day cycles. The recommended capecitabine starting dose is 1250 mg/m^2 twice daily (equivalent to 2500 mg/m^2 total daily dose) per the package insert, and subsequent treatment will be dictated by tolerance and institutional practice.
Eligibility Criteria	Inclusion Criteria Patients may be included in the study only if they meet all of the following inclusion criteria at the time of randomization: 1. Female or male subjects with metastatic, histologically or cytologically confirmed carcinoma of the breast. 2. Documented progression of disease, based on radiographic, clinical or pathologic assessment showing increased tumor burden or new site(s) of disease during or subsequent to the last anticancer regimen received. 3. Overexpression of GPNMB (≥ 25% of malignant epithelial cells expressing GPNMB, as determined by a central laboratory using IHC methods) in at least one tumor sample obtained in the advanced setting. 4. Triple-negative status determined in a tumor sample obtained in the advanced setting, according to the following criteria: a. Minimal or no expression of estrogen and progesterone receptors (<10% of cells positive by immunohistochemistry (IHC)). Patients with low hormone receptor expression (ER and/or PR 1-9%) must be deemed appropriate candidates for cytotoxic chemotherapy by the investigator. b. Minimal or no expression of HER2 (IHC staining of 0 or 1+; ISH single-probe average HER2 copy number < 4.0 signals/cell; or ISH dual-probe HER2/CEP17[a] ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell). (Wolff, Hammond et al. 2014):

[a]Also referred to as CEN17.

NOTE: laboratory reports will be required to provide quantitative results of sufficient detail to verify the above eligibility for all patients enrolled.

5. 0 to 2 prior chemotherapy-containing regimens for advanced breast cancer. For the purpose of this criterion, a regimen is defined as any combination of therapy, including sequential therapy, received before progression.
6. Prior receipt of anthracycline-containing chemotherapy in any setting, unless anthracycline therapy is not clinically indicated, in the opinion of the treating investigator
7. Prior receipt of taxane-containing chemotherapy, in any setting
8. Age ≥ 18 years
9. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (**Appendix 4**).
10. Life expectancy of ≥ 3 months
11. Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (**Appendix 3**). Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.
12. Resolution of all chemotherapy or radiation-related toxicities ≤ CTCAE v. 4.0 Grade 1 severity, except for alopecia.
13. Adequate bone marrow function as assessed by absolute neutrophil count (ANC) ≥1500/mm^3; hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm^3.
14. Adequate renal function as assessed by serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance > 40 mL/min per the Cockcroft and Gault formula (**Appendix 5**).
15. Adequate liver function as assessed by total bilirubin ≤ 1.5 x upper limit of normal (ULN), and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 x ULN (≤ 5.0 x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.
16. Read, understood, and provided written informed consent and, if applicable, HIPAA authorization.

Exclusion Criteria

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

1. Progression/recurrence of breast cancer during or within 3 months of completion of neoadjuvant or adjuvant chemotherapy.
2. Investigational therapy within four weeks before planned start of study treatment.
3. Persistent neuropathy > NCI-CTCAE v. 4.0 Grade 1 (at randomization).
4. 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.
5. Known hypersensitivity to 5-flourouracil, capecitabine or any of its components.
6. Known dihydropyrimidine dehydrogenase (DPD) deficiency.
7. Known brain metastases, unless previously treated and asymptomatic for 2 months and not progressive in size or number for 2 months prior to randomization. Continued use of steroids and/or anticonvulsants (in the absence of any suspicion of progressive brain metastases) is acceptable.

	8. Subjects unable to provide informed consent and/or unable to comply with the study procedures. 9. Pregnant or breast-feeding women, and women or men who are not willing to use effective contraception during the time from signing of informed consent through two months after the last dose of study treatment. Effective contraception is defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge or vaginal ring), intra-uterine device (IUD), implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement. 10. Previously received capecitabine and discontinued due to progressive disease or intolerance; previously received CDX-011 (CR011-vcMMAE; glematumumab vedotin) or other MMAE-containing agents. ~~[criterion deleted]~~ 11. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment. ~~[criterion deleted]~~ 12. Chronic use of systemic corticosteroids above the physiologic dose (5 mg per day prednisone or equivalent) within 7 days of enrollment, except for premedication. ~~[criterion deleted]~~ 13. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, and congestive heart failure (New York Heart Association class 3 or 4), a history of a serious uncontrollable arrhythmia despite treatment, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry. 14. Any underlying medical condition that, in the investigator's opinion, will make the administration of study treatment (CDX-011 or capecitabine) hazardous to the patient, or would obscure the interpretation of adverse events. 15. Other malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or any other cancer from which the patient has been disease-free for ≥ 5 years.
Criteria for Evaluation	<u>Safety evaluations:</u> Safety will be assessed by vital sign measurements, clinical laboratory tests, ECGs, physical examinations and the incidence and severity of adverse events (graded according to CTCAE v 4.0.). <u>Anti-tumor activity evaluations:</u> Anti-tumor activity will be assessed via PFS, ORR, DOR and OS. Tumor response and progression will be defined by an independent review committee, according to RECIST 1.1 criteria. <u>Immunogenicity:</u> Patients will be monitored for the development of anti-CDX-011 and anti-CR011 antibodies, and whether these antibodies are neutralizing. <u>Pharmacokinetics:</u>

	Concentration of the antibody-drug conjugate (ADC), total antibody (TA) and free MMAE will be determined using GLP compliant enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Population PK analyses will be performed to obtain pharmacokinetic parameters and to explore the relationships between patient-specific measures of exposure and safety and activity parameters; the influence of key intrinsic factors, such as weight and gender, on variability in PK will also be evaluated. The impact of circulating GPNMB levels on pharmacokinetic parameters may also be examined. Pharmacodynamics: Pharmacodynamics will be evaluated via assessment of tumor tissue obtained via voluntary biopsy or re-resection. Parameters evaluated may include localization of CDX-011, CR011 or MMAE at the tumor site and/or GPNMB expression levels in tumor tissue, as well evaluation of tumor infiltrating leukocytes. Soluble GPNMB levels in the circulation may also be examined.
Statistical Methods	The primary efficacy analysis will be performed in accordance with the intention-to-treat principle. All randomized patients will be included in the primary efficacy analysis according to their assigned study treatment, irrespective of the actual treatment received. The primary analysis of safety will include all patients who receive at least 1 dose of study treatment. The primary efficacy endpoint will be PFS. PFS is defined as the time from randomization to the earlier of disease progression or death due to any cause. The primary analysis of PFS will be based on PFS events determined by the IRC according to RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009). Patients whom enter hospice care, or other such similar end-of-life care, without prior objective evidence of disease progression will be considered to have disease progression for purposes of the primary analysis of PFS. Unless specified otherwise, all recorded PFS events will be included in the primary analysis regardless of stopping randomized therapy. Patients who initiate alternate anticancer therapy in the absence of documented progression will be censored at the latest disease assessment prior to initiation of such therapy. Patients who were last known to be alive and progression-free will be censored at the latest disease assessment. Patients with no baseline or post-baseline disease assessments will be censored at the randomization date unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event). A secondary analysis of PFS will be performed based on PFS events determined by the local investigator. Sensitivity analyses will be performed to assess the impact of the different censoring mechanisms and deviations from the planned schedule of disease assessments. PFS will be summarized descriptively using the Kaplan-Meier method. The primary inferential comparison between treatment arms will use the log-rank test stratified by the randomization stratification factors. The hazard ratio for treatment will be estimated using a stratified Cox proportional hazards model. For patients with metastatic advanced GPNMB-expressing breast cancer in the treatment setting under investigation, median PFS of 4 months is anticipated following randomization to capecitabine. It is hypothesized that CDX-011 will increase median PFS in such patients by 2.25 months (i.e., 4.0 vs 6.25 months). Under the assumption of proportional hazards, such an increase corresponds to a hypothesized hazard ratio of 0.64. If this hypothesized hazard ratio is true, 203 PFS events (total of two arms) determined by IRC will provide 85% power with 2-sided type I error of 0.05. Under the assumption

	of exponential distribution for each arm and uniform enrollment over 2 years, and 10% drop out rate (PFS events cannot be observed), 300 patients (200 in the CDX-011 arm and 100 in the capecitabine arm) are needed, and it is anticipated that 203 PFS events will be observed in approximately 26 months from the date the first patient is randomized. The sample size calculation is performed using SAS v9.4. Secondary efficacy endpoints are ORR, DOR and OS. ORR is defined as the proportion of patients who achieve a best overall response of complete or partial response (CR or PR) according to RECIST 1.1. Inferential comparisons between treatment arms will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. The duration of objective response will be summarized descriptively using the Kaplan-Meier method.

4. SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Assessments

Visit	Screening[2]	Treatment Visits[3]							Disease Assessment Visit[4]	Survival Assessment[5]
		Cycle 1/ Day 1	Cycle 1/ Day 7	Cycle 1/ Day 14	Cycle 2/ Day 1	Cycles 3, 5, 7, etc. ("odd cycles") / Day 1	Cycles 4, 6, 8, etc. ("even cycles")/ Day 1	End of Treatment[6]		
Visit window[1]	*Day -28 to Day -1*		*+/-1 day*	*+/-1 day*	*+/-3 days*	*+/-5 days*	*+/-5 days*	*Within 28 days post-dosing*	*Every 6 (±1) weeks for 6 months and every 9 (±2) weeks thereafter, until progression.*	*Every 12 (±2) weeks until study closure*
Informed Consent and, if applicable, HIPAA	X									
Tumor tissue[8]	X[9]			X[10]						
Determination of TNBC status[11]										
Medical history[12]	X	X								
Physical examination[13]	X	X[7]			X	X	X	X		
Vital signs[14]	X	X[7]			X	X	X	X		
ECOG performance status	X	X[7]			X	X	X	X		
Electrocardiogram (ECG) [15]	X[15]	X[7,15]						X[15]		
Pregnancy test	X[16]	X[7,16]								
Hematology[17]	X	X[7]	X	X	X	X	X	X		
Blood chemistry[17]	X	X[7]			X	X	X	X		
Urinalysis[17]	X	X[7]				X		X		
Immunogenicity[18]		X[19]				X[19]		X[19]		
Pharmacokinetics[18]		X[20]			X[20]	X[20]	X[20]	X[20]		
PBMC collection[18]		X[21]			X[21]			X		
Molecular profiling[22]		X[22]								
Questionnaire (EORTC QLQ-C30)[23]	X	X[7]				X		X		
Disease assessment[24]	X								X[24]	
Randomization[25]	X									
Administration of study treatment[26]		X			X	X	X			

Survival status										X
Concomitant medication review[27]	X	X			X	X	X	X	X[27]	X[27]
Adverse event monitoring[28]		X	X[29]	X[29]	X	X	X	X	X[30]	X[30]

(footnotes on next page)

Table 1 - Footnotes:

1. A delay in study treatment or performance of study visits due to holidays, weekends, inclement weather or other unforeseen circumstances will be permitted and not considered a protocol violation. However, significant delays (i.e., greater than one week) should be discussed with the study medical monitor to reach consensus on subsequent scheduling.
2. No study procedures will be performed prior to receipt of signed Informed Consent. However, assessments performed according to standard of care prior to receipt of Informed Consent may be utilized to fulfill the screening requirement, if completed within the required window for screening.
3. Patients will receive CDX-011 or capecitabine (on a three-week cycle) until intolerance or progression of disease.
4. Disease assessments will be performed every six weeks (+/- 1 week) for six months (i.e., weeks 6, 12, 18, 24), every 9 weeks (+/- 2 weeks) thereafter (i.e., weeks 33, 42, 51, 60, 69, 78, etc.), until progression. Patients who discontinue study treatment without documented progression of disease as per RECIST 1.1 should continue to have Disease Assessment Visits until such criteria are met (regardless of intervening therapy). In the event that follow-up is discontinued without a final disease assessment documenting objective disease progression, the reason must be supplied; in particular, any admittance to hospice or other such similar end-of-life care must be reported. If a partial or complete response is noted, a follow-up radiographic assessment must be done no sooner than 28 days later to confirm response. If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously non-resectable tumor), these interventions should be avoided if clinically feasible until after the 12 week response assessment. Prior to any intervention (such as surgical resection, palliative radiation or alternate anti-cancer therapy), every effort should be made to perform a tumor response assessment in order to document progression and/or confirm an objective response. Patients who undergo surgical resection or radiation in the absence of progression may continue to receive study treatment until remaining lesions meet criteria for progression of disease.
5. Subsequent to the End of Treatment Visit, all patients will be followed at 12 (±2) week intervals until study closure. These visits may be performed by telephone. However, for patients who discontinue study treatment in the absence of progression, survival assessments may be combined with Disease Assessment Visits, and conducted every 6 (±1) or 9 (±2) weeks until progression, and then at 12 (±2) week intervals until study closure.
6. The End of Treatment Visit should be performed within 28 days after last dose of study treatment and prior to initiation of alternate therapies.
7. Assessments do not need to be repeated if completed within the previous 24 hours as part of the screening assessment.
8. Assessment of GPNMB expression (by IHC) will be performed at a central laboratory. Additional analyses to be performed centrally may also include GPNMB expression by RT-PCR, examination of tumor markers using IHC or other molecular analyses, evaluation of tumor infiltrating leukocyte populations, biomarkers related to immune activation, and localization of CDX-011, CR011, or MMAE at the tumor site. Sample collection, processing and shipping instructions will be provided separately.
9. Tumor specimen(s) submitted for screening must have been obtained in the setting of advanced disease. Submission of additional samples from other collection dates, when available, is encouraged. Tissue may be submitted and tested at any time prior to or during the 28-day window for screening, provided that the patient has signed an appropriate consent (either a tumor tissue-specific consent or full study consent).
10. In the event of a repeat resection or biopsy during treatment or following progression, submission of tissue sample for central analysis is strongly encouraged.
11. Determination of triple-negative status will be done at a local laboratory. Tumor sample(s) used to determine eligibility must be obtained in the setting of advanced disease. Laboratory reports will be required to provide quantitative results of sufficient detail to verify eligibility for all patients enrolled (see study entry criteria).
12. Medical history includes demography, race, ethnicity, history of breast cancer, previous therapy, and pre-existing diseases. At Cycle 1, Day 1, medical history is updated with any adverse events occurring prior to administration of study drug.
13. Complete physical exam should be performed at screening; thereafter, symptom-directed exams are acceptable.

14. Vital signs to include height (at screening only), weight, respiration, pulse, temperature, and resting systolic and diastolic blood pressure. For patients receiving CDX-011, vital signs should be assessed pre-infusion, at 45 (±15) minutes during the infusion, and within one-half hour following completion of the infusion. (Note: weight is only assessed once per visit.) For patients receiving capecitabine, vital signs should be assessed once at the indicated visits.
15. A second original copy of the ECG tracing should be retained for possible submission to Celldex.
16. Serum or urine pregnancy test only for women of childbearing potential. Patients of non-childbearing potential include those who are ≥60 years, surgically sterilized, or postmenopausal with absence of menses for at least 1 year. However, women <60 with therapy-induced amenorrhea will require a pregnancy test unless additional evidence (oophorectomy or serial measurement of FSH and/or estradiol) are available to ensure postmenopausal status.
17. Laboratory assessments will include the following, when indicated. Hematology results must be reviewed prior to dosing.

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

18. Analyses will be performed by centralized laboratories. Sample collection, processing and shipping instructions will be provided separately.
19. Samples drawn only for patients receiving CDX-011. On CDX-011 dosing days, samples are collected prior to dosing.
20. Samples for pharmacokinetic analyses will be collected for CDX-011-treated patients only. Analysis may also include circulating GPNMB or other soluble mediators. At each CDX-011 dosing day, samples will be collected prior to dosing and at end of infusion (at or within 15 minutes of completion of infusion).
21. PBMC collection will occur for up to 150 patients enrolled at a subset of study centers in the United States (regardless of treatment arm). On CDX-011 dosing days, samples are collected prior to dosing. Analysis will include examination of GPNMB expression on myeloid suppressor cells. Celldex will notify the sites when the requisite number of patients providing PBMC samples has been reached or that further data is not needed.
22. Blood sample will be stored for retrospective BRCA1/2 mutation status and other potentially relevant molecular markers.
23. EORTC QLQ-C30 Questionnaire (**Appendix 6**) completed only for patients who are fluent in a language in which the questionnaire is validated (information will be provided by Celldex). Each questionnaire must be completed by the patient prior to any other assessments or procedures for that visit. It should be completed without assistance if possible. If the patient requires assistance to complete the questionnaire, the assistance should be provided by clinical or study staff as opposed to family members or significant others, and the nature of required assistance should be documented. If a scheduled questionnaire is missed, the patient should complete the questionnaire at the next study visit
24. Imaging-based evaluation per RECIST 1.1 should be performed in accordance with the Site Manual provided by Celldex (or designee). Contrast-enhanced CT of the chest, abdomen, and pelvis, as well as all other suspected disease sites is required. MRI exams of the brain, abdomen, and pelvis can be performed in lieu of a CT; however MRI exams of the chest are not recommended. In the event that a chest MRI is performed, a non-contrast chest CT is strongly recommended to evaluate the lung parenchyma. Brain and/or bone scans are required for any patients with a history of metastases to bone and/or brain or where symptomatology raises the suspicion for bone and/or brain metastases. Lesions identified on bone scans should be confirmed by a CT or MRI at baseline, and, if identified as target lesions due to soft tissue component, they should continue to be

followed by the same methodology (i.e., CT or MRI scan). However, bone lesions followed as non-target disease may be subsequently followed by bone scans only. Lesions that cannot be imaged but are assessable by clinical exam may be assessed using color photography including a ruler (preferred method) or measured with calipers. Normally, all target and non-target disease sites should be evaluated at each assessment. However, for patients with non-target bone disease, bone scans need only be repeated every twelve weeks. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.

25. Randomization may be performed up to 5 days prior to initiation of study treatment, but should occur only after confirming all eligibility criteria have been met.
26. Unless otherwise specified, all study assessments should be performed prior to administration of study treatment, and may be performed up to 24 hours prior to treatment administration if assessments remain within the specified visit window.
27. All concomitant medication will be documented in the CRF if taken within 28 days prior to Study Day 1, and either (whichever occurs sooner): a) 28 days after last dose of study treatment or b) initiation of alternate anti-cancer therapy. In addition, all anti-cancer medications and concomitant medications required to treat CDX-011-related SAEs taken throughout the duration of study follow-up should also be recorded.
28. For patients who develop grade 3 rash possibly related to CDX-011 and who provide appropriate consent, punch biopsies and photographs of the rash site, as well as uninvolved skin, are strongly encouraged. Samples may be submitted for central analyses including quantification of GPNMB expression; in these cases, collection, processing and shipping instructions will be provided separately.
29. Adverse event monitoring on Cycle 1 Day 7 and Cycle 1 Day 14 can be performed in person or by telephone to determine if the patient is experiencing any adverse events.
30. Events occurring > 28 days after discontinuation of study treatment are only reportable if serious (SAE) and potentially treatment-related.

6. STUDY OBJECTIVES

The primary objective of the study is to evaluate the anti-cancer activity of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer as measured by the duration of progression-free survival (PFS).

Secondary objectives are:

- To further assess the anti-cancer activity of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer, as assessed by the objective response rate (ORR), duration of response (DOR) and overall survival (OS).
- To further characterize the safety of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer.
- To obtain pharmacokinetic parameters and to explore the relationships between patient-specific measures of exposure and safety and activity parameters

An exploratory objective is:

- To assess whether treatment with CDX-011 is associated with improvement in quality of life and/or cancer-related pain as reflected by reduced analgesic use.

7. INVESTIGATIONAL PLAN

7.1. Overall Design and Plan of the Study

This is a pivotal, open-label, prospectively controlled, randomized study of CDX-011 in patients with metastatic GPNMB-expressing triple negative breast cancer. Eligible patients will be randomized (2:1) to receive CDX-011 or capecitabine. Enrollment will be stratified as follows:

- 0-1 prior line of chemotherapy for advanced disease vs. 2 prior lines of chemotherapy for advanced disease

- Progression-free interval ≤ 6 months after receipt of taxane therapy vs. progression-free interval > 6 months after receipt of taxane therapy
- Received anthracycline therapy previously vs. no prior anthracycline therapy

Study treatment, and associated study visits at 3 week intervals, will continue until disease progression or intolerance. Tumor assessments will be performed at six week intervals for six months and nine week intervals thereafter, until disease progression. Upon discontinuation of study treatment, patients will be permitted to receive appropriate alternate anti-cancer therapies and will be followed for progression-free survival (if progression is not yet documented) and overall survival.

The study analyses of PFS, ORR and DOR will be based on tumor response assessments performed by an independent review committee according to RECIST 1.1 guidelines (Eisenhauer, Therasse et al. 2009) (**Appendix 3**). The investigator's assessment of tumor response (according to RECIST 1.1) will guide clinical management and eligibility for continuation of study treatment.

An independent data monitoring committee will review cumulative data on an interim basis. The interim data reviews may include but are not limited to summaries of adverse events, laboratory values and vital signs. The IDMC will conduct reviews approximately every 6 months, or as frequently as deemed necessary by the IDMC, starting from the first randomized patient. If a safety concern is identified, the IDMC may recommend modifying, halting or permanently stopping the trial at any time.

7.2. Selection of Study Population

7.2.1. Number of Patients

Approximately 300 patients will be enrolled (randomized 2:1 to CDX-011 or capecitabine).

7.2.2. Subject Eligibility

7.2.2.1. Inclusion Criteria

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

1. Female or male subjects with metastatic, histologically or cytologically confirmed carcinoma of the breast.
2. Documented progression of disease, based on radiographic, clinical or pathologic assessment showing increased tumor burden or new site(s) of disease during or subsequent to the last anticancer regimen received.
3. Overexpression of GPNMB (≥ 25% of malignant epithelial cells expressing GPNMB, as determined by a central laboratory using IHC methods) in at least one tumor sample obtained in the advanced setting.
4. Triple-negative status confirmed in a tumor sample obtained in the advanced setting, according to the following criteria:
   a. Minimal or no expression of estrogen and progesterone receptors (<10% of cells positive by immunohistochemistry (IHC)). Patients with low hormone receptor expression (ER and/or PR 1-9%) must be deemed appropriate candidates for cytotoxic chemotherapy by the investigator.

b. Minimal or no expression of HER2 (IHC staining of 0 or 1+; ISH single-probe average HER2 copy number < 4.0 signals/cell; or ISH dual-probe HER2/CEP17[b] ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell). (Wolff, Hammond et al. 2014)

NOTE: laboratory reports will be required to provide quantitative results of sufficient detail to verify the above eligibility for all patients enrolled.

5. 0 to 2 prior chemotherapy-containing regimens for advanced breast cancer. For the purpose of this criterion, a regimen is defined as any combination of therapy, including sequential therapy, received before progression.
6. Prior receipt of anthracycline-containing chemotherapy in any setting, unless anthracycline therapy is not clinically indicated, in the opinion of the treating investigator.
7. Prior receipt of taxane-containing chemotherapy, in any setting
8. Age ≥ 18 years
9. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 (**Appendix 4**).
10. Life expectancy of ≥ 3 months.
11. Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (**Appendix 3**). Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.
12. Resolution of all chemotherapy or radiation-related toxicities ≤ CTCAE v. 4.0 Grade 1 severity, except for alopecia.
13. Adequate bone marrow function as assessed by absolute neutrophil count (ANC) ≥1500/mm^3; hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm^3.
14. Adequate renal function as assessed by serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance > 40 mL/min per the Cockcroft and Gault formula (**Appendix 5**).
15. Adequate liver function as assessed by total bilirubin ≤ 1.5 x upper limit of normal (ULN), and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 x ULN (≤ 5.0 x ULN in the case of liver metastases). Patients with known Gilbert's syndrome may be enrolled with total bilirubin ≤ 3.0 mg/dL.
16. Read, understood, and provided written informed consent and, if applicable, HIPAA authorization.

7.2.2.2. Exclusion Criteria

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

1. Progression/recurrence of breast cancer during or within 3 months of completion of neoadjuvant or adjuvant chemotherapy.
2. Investigational therapy within four weeks before planned start of study treatment.
3. Persistent neuropathy > NCI-CTCAE v. 4.0 Grade 1 (at randomization).
4. 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.
5. Known hypersensitivity to 5-flourouracil, capecitabine or any of its components.

[b] Also referred to as CEN17.

6. Known dihydropyrimidine dehydrogenase (DPD) deficiency.
7. Known brain metastases, unless previously treated and asymptomatic for 2 months and not progressive in size or number for 2 months prior to randomization. Continued use of steroids and/or anticonvulsants (in the absence of any suspicion of progressive brain metastases) is acceptable.
8. Subjects unable to provide informed consent and/or unable to comply with the study procedures.
9. Pregnant or breast-feeding women, and women or men who are not willing to use effective contraception during the time from signing of informed consent through two months after the last dose of study treatment. Effective contraception is defined as double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge or vaginal ring), intra-uterine device (IUD), implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.
10. Previously received capecitabine and discontinued due to progressive disease or intolerance; previously received CDX-011(CR011-vcMMAE; glembatumumab vedotin) or other MMAE-containing agents. ~~[criterion deleted]~~
11. Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment. ~~[criterion deleted]~~
12. Chronic use of systemic corticosteroid above the physiologic dose (5 mg per day prednisone or equivalent) within 7 days of enrollment, except for premedication. ~~[criterion deleted]~~
13. Significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, and congestive heart failure (New York Heart Association class 3 or 4), a history of a serious uncontrollable arrhythmia despite treatment, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry.
14. Any underlying medical condition that, in the investigator's opinion, will make the administration of study treatment (CDX-011 or capecitabine) hazardous to the patient, or would obscure the interpretation of adverse events.
15. Other malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or any other cancer from which the patient has been disease-free for ≥ 5 years.

7.2.3. Measures to Minimize Bias

This is a randomized, controlled, open-label study. In an effort to minimize bias in the interpretation of tumor response and progression-free survival, these analyses will be based on tumor response assessments performed by an external, independent review committee according to standardized, objective response criteria (RECIST 1.1), blinded to treatment allocation and investigator assessments.

7.2.4. Withdrawals and Replacement of Patients

Every effort should be made within the bounds of safety and patient choice to have each patient complete the study. As this study utilizes an Intent-to-Treat analysis, there will be no replacement of randomized patients.

An explanation will be recorded for each patient taken off study treatment or discontinuing the study.

7.2.4.1. Discontinuation of Study Treatment

Reasons for discontinuation of study treatment include:

- Progressive disease, as assessed by the treating investigator in accordance with RECIST 1.1 criteria (**Appendix 3**);
- Symptomatic deterioration (clinical progression);
  - Note: This category is applicable to patients with a global deterioration of health status requiring discontinuation of treatment. However, per RECIST 1.1 (See **Appendix 3**), symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. Thus, every effort should be made to continue disease assessments per protocol until documented objective progression, regardless of any changes in therapy.
- Receipt of alternate anti-cancer treatments;
- Withdrawal request by the patient or the patient's legal representative;
  - Note: Withdrawal of consent for continued treatment should be differentiated from withdrawal of consent for study follow-up, and every effort should be made within the bounds of safety and patient choice to have each patient complete the study follow-up.
- Adverse Event, including the development of dose limiting toxicity (See **Section 8.1.6**);
- Physician Decision;
- Non-compliance of the patient;
- Pregnancy;
- Death, otherwise not explainable by the above options;
- Patient lost to follow-up. (See below.)

Patients who discontinue CDX-011 should be seen for an End of Treatment Visit. Patients who discontinue study treatment without progression of disease as per RECIST 1.1 should continue Disease Assessment Visits until criteria for disease progression are met. (See**Table 1**.)

7.2.4.2. Discontinuation from Study

Reasons for patient removal from the study include:

- Withdrawal request by the patient or the patient's legal representative (withdrawal of consent for the study follow-up);
- Patient lost to follow-up. A subject should be considered lost to follow up only after multiple efforts have been made to contact the subject to assess his/her health status after failure of the subject to attend scheduled visits. If after 2 documented phone calls the investigative site is still unable to contact the subject, a certified letter should be sent to his/her home for immediate response. If there is still no response, the subject is to be considered lost to follow

up. A record of the subject being lost to follow up should be noted in the source documents along with the phone contacts and the returned certified mail (if sent back).

7.2.5. Completion of Study

It is anticipated that the enrollment period will be approximately 2 years. All patients will be followed with regard to survival until death, discontinuation from study follow-up, or termination/completion of study. Patients who die or complete the study follow-up through study closure will be considered to have "completed" the study. The study will be declared complete when sufficient data is obtained to conclude the study.

Premature termination of this study may occur because of a regulatory authority decision, drug safety issues, or at the discretion of Celldex. In addition, Celldex retains the right to discontinue development of CDX-011 at any time.

8. STUDY TREATMENT

[redacted]

8.2. Capecitabine

8.2.1. Description, Packaging, Labeling, Accountability and Storage

Capecitabine will be obtained from commercial supply and handled/stored in a fashion consistent with package insert and institutional policies. Generic capecitabine may be utilized. The following sections are based on package insert recommendations (Feb 2011). However, investigators are responsible for referencing the complete and most current package insert for full guidance regarding potential toxicity and dosing of capecitabine.

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.

Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg of capecitabine and each peach-colored tablet contains 500 mg of capecitabine. The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

8.2.2. Compliance

Compliance with self-administered oral agents (i.e., capecitabine) will be assessed by patient report.

8.2.3. Administration

Dose Calculation

Capecitabine dose is calculated according to body surface area.

Table 5. Capecitabine Dose Calculation According to Body Surface Area

Dose Level 1250 mg/m^2 Twice a Day		Number of Tablets to be Taken at Each Dose (Morning and Evening)	
Surface Area (m^2)	**Total Daily Dose* (mg)**	**150 mg**	**500 mg**
≤ 1.25	3000	0	3
1.26-1.37	3300	1	3
1.38-1.51	3600	2	3
1.52-1.65	4000	0	4
1.66-1.77	4300	1	4
1.78-1.91	4600	2	4
1.92-2.05	5000	0	5
2.06-2.17	5300	1	5
≥ 2.18	5600	2	5

*Total Daily Dose divided by 2 to allow equal morning and evening doses

Dosing and Administration

Investigators are encouraged to follow the recommended dosing from the Capecitabine Package Insert and NCCN Guidelines (available on-line at www.nccn.org), as well as institutional standard. The recommended starting dose of capecitabine per the package insert is 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period, given as 3-week cycles. Subsequent treatment will be dictated by tolerance and institutional practice, with consideration to the guidance below.

In patients with moderate renal impairment (baseline creatinine clearance = 40 to 50 mL/min [Cockroft and Gault; **Appendix 5**]), a dose reduction to 75% of the capecitabine starting dose (from 1250 mg/m^2 to 950 mg/m^2 twice daily) is recommended. Subsequent dose adjustment is recommended as outlined in**Table 6.** No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min).

Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal.

8.2.4. Dose Modifications

Capecitabine dosage may need to be individualized to optimize patient management. Patients should be carefully monitored for toxicity and doses of capecitabine should be promptly modified as necessary to accommodate individual patient tolerance to treatment. Toxicity due to capecitabine administration may be managed by symptomatic treatment, dose interruptions and adjustment of capecitabine dose. Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.

Management of capecitabine toxicity, dosing, dose reductions and supportive care should be consistent with the package insert recommendations, but should be dictated by institutional and investigator standard practice and the need for individual patient management. **Table 6** outlines

the recommended capecitabine dose modification scheme for the management of adverse reactions.

Table 6. Recommended Dose Modifications of Capecitabine

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
Grade 1		
	Maintain dose level	Maintain dose level
Grade 2		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	-
Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	-
Grade 4		
-1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

*National Cancer Institute of Canada Common Toxicity Criteria were used except for the hand-and-foot syndrome (see **Section 8.2.5.4**).

8.2.5. Potential Toxicity and Management of Toxicity

Management of toxicity associated with the administration of capecitabine is discussed below. Investigators should always refer to the current capecitabine package insert for further information and current guidance.

The most common side effects of capecitabine are:

- Diarrhea, nausea, vomiting, stomatitis, abdominal pain, upset stomach, constipation, loss of appetite, and dehydration. These side effects are more common in patients age 80 and older.
- Hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss
- Tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems

8.2.5.1. Diarrhea

Capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. In 875 patients with either metastatic breast or colorectal cancer who received capecitabine monotherapy, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4 diarrhea was 5 days.

National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support.

If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following a reoccurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea, subsequent doses of capecitabine should be decreased. Standard antidiarrheal treatments (e.g., loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

8.2.5.2. Nausea/Vomiting

Patients experiencing ≥grade 2 nausea (food intake significantly decreased but able to eat intermittently) and/or ≥ grade 2 vomiting (2 to 5 episodes in a 24-hour period) should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

8.2.5.3. Cardiotoxicity

The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

8.2.5.4. Hand-and-Foot Syndrome

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving capecitabine monotherapy in the metastatic setting.

Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If grade 2 or 3 hand-and-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of capecitabine should be decreased.

8.2.5.5. Stomatitis

Patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

8.2.5.6. Fever and Neutropenia

Patients who develop a fever of 100.5°F or greater or other evidence of potential infection should be instructed to call their physician.

8.2.5.7. Hyperbilirubinemia

In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of capecitabine 1250 mg/m^2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period, grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of patients. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also had post-baseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had post-baseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both pre-baseline and post-baseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

In the 596 patients treated with capecitabine as first-line therapy for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of capecitabine monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and median total bilirubin increased from 8 μm/L at baseline to 13 μm/L during treatment with capecitabine. Of the 136 colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

In 251 patients with metastatic breast cancer who received a combination of capecitabine and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).

If drug-related grade 3 to 4 elevations in bilirubin occur, administration of capecitabine should be immediately interrupted until the hyperbilirubinemia decreases to ≤3.0 X ULN.

8.2.5.8. Hematologic

In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m^2 administered twice daily as monotherapy for 2 weeks followed by a 1-week rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in hemoglobin, respectively. In 251 patients with metastatic breast cancer who received a dose of capecitabine in combination with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 9.6% had grade 3 or 4 anemia.

Patients with baseline neutrophil counts of < 1.5 x 10^9/L and/or thrombocyte counts of < 100 x 10^9/L should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 hematologic toxicity, treatment with capecitabine should be interrupted.

8.2.5.9. Drug-drug interactions

8.2.5.9.1 Anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. These events occurred in

patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly.

8.2.5.9.2 Phenytoin (Dilantin®)

The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need to be reduced. Post-marketing reports indicate that some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites.

8.2.5.9.3 Leucovorin

The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

8.2.5.9.4 CYP2C9 substrates

Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is coadministered with CYP2C9 substrates.

8.2.6. Additional Warnings and Precautions

8.2.6.1. Drug-Food Interaction

Food was shown to reduce both the rate and extent of absorption of capecitabine. In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. It is recommended that capecitabine be administered with food.

8.2.6.2. Dihydropyrimidine Dehydrogenase Deficiency

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-fluorouracil therefore cannot be excluded. Patients with DPD deficiency are not eligible for this trial.

8.2.6.3. Renal Insufficiency

Patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance < 30 mL/min) renal impairment showed higher exposure for capecitabine, 5-FDUR, and FBAL than in those with normal renal function. Patients with moderate renal impairment at baseline require dose reduction (see **Section 8.2.2**). Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a grade 2 to 4 adverse event as outlined in **Table 6**.

8.2.6.4. Hepatic Insufficiency

Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is not known.

8.2.6.5. Geriatric Patients

Patients ≥80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875 patients with either metastatic breast or colorectal cancer who received capecitabine monotherapy, 62% of the 21 patients ≥80 years of age treated with capecitabine experienced a treatment-related grade 3 or 4 adverse event: diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no patients were >80 years of age) treated with capecitabine in combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.

Among the 67 patients ≥60 years of age receiving capecitabine in combination with docetaxel, the incidence of grade 3 or 4 treatment-related adverse reactions, treatment-related serious adverse reactions, withdrawals due to adverse reactions, treatment discontinuations due to adverse reactions and treatment discontinuations within the first two treatment cycles was higher than in the <60 years of age patient group.

In 995 patients receiving capecitabine as adjuvant therapy for Dukes' C colon cancer after resection of the primary tumor, 41% of the 398 patients ≥65 years of age treated with capecitabine experienced a treatment-related grade 3 or 4 adverse event: hand-and-foot syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3.0%), neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%) patients. In patients ≥65 years of age (all randomized population; capecitabine 188 patients, 5-FU/LV 208 patients) treated for Dukes' C colon cancer after resection of the primary tumor, the hazard ratios for disease-free survival and overall survival for capecitabine compared to 5-FU/LV were 1.01 (95% C.I. 0.80 – 1.27) and 1.04 (95% C.I. 0.79 – 1.37), respectively.

Physicians should exercise caution in monitoring the effects of capecitabine in the elderly. Insufficient data are available to provide a dosage recommendation.

8.2.6.6. Pregnancy/Nursing Mothers

Capecitabine may cause fetal harm when given to a pregnant woman, and it is not known whether this drug is excreted in human milk. Pregnant and nursing mothers are not eligible for participation in this study. Women of childbearing potential and their partners who are admitted to the clinical study must take adequate contraceptive measures.

9. CONCOMITANT THERAPY

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

The effect of CDX-011 on the absorption, metabolism, or excretion of other drugs has not been studied. Drugs known to strongly inhibit CYP3A4 should be used with caution, and drugs known

to be potent CYP3A4 inducers should be avoided, if at all possible, while patients are exposed to CDX-011 (see **Section 8.1.8.2**). Drug-drug interactions of concern for capecitabine include anticoagulants, phenytoin, leucovorin, and CYP2C9 substrates. See **Section 8.2.5.9** for further information.

Prolonged use of systemic corticosteroids above the physiologic dose (5 mg prednisone or equivalent) should be avoided during the study.

Subjects may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. During study treatment, patients may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management. Antiemetics and steroids for chemotherapy premedication are also permitted. Growth factor support is permitted and should be administered with consideration to the American Society of Clinical Oncology (ASCO) guideline on the use of hematopoietic colony-stimulating factors (Smith, Khatcheressian et al. 2006). Efforts should be made to maintain stable doses of concomitant medications during the course of treatment with CDX-011.

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

All concomitant medication will be documented in the CRF if taken within 28 days prior to randomization, and either (whichever occurs sooner): a) 28 days after last dose of study treatment (either CDX-011 or capecitabine chemotherapy), or b) initiation of alternate anti-cancer therapy. All anti-cancer medications taken throughout the duration of study follow-up (including the initiation of anti-cancer medications representing the reason for discontinuation of treatment or study) should also be recorded, as should concomitant medications required to treat CDX-011-related SAEs.

10. STUDY PROCEDURES

10.1. Schedule of Investigations and Data Collection

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

10.1.1. Screening Period

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

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

10.1.2. Study Randomization / Treatment Assignment

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

Randomization should occur only after confirming all inclusion criteria and none of the exclusion criteria have been met. The study center will randomize the patient to treatment according to instructions provided by Celldex Therapeutics, Inc. (or designee).

10.1.3. Treatment Phase

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

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

10.1.4. Disease Assessment Visits

Disease assessments will be performed every 6 (±1) weeks for 6 months and every 9 (±2) weeks thereafter, until progression. Patients who discontinue study treatment without documented progression of disease as per RECIST 1.1 should continue to have Disease Assessment Visits until such criteria are met, regardless of intervening changes in therapy.

10.1.5. Survival Follow-up

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

10.2. Methods of Assessment

10.2.1. Activity

10.2.1.1. Anti-tumor Activity

Anti-tumor activity will be assessed via PFS, ORR, DOR, and OS. Tumor response and progression will be defined by the independent review committee, according to RECIST 1.1 criteria.

10.2.1.2. Immunogenicity

Patients will be monitored for the development of anti-CDX-011 and anti-CR011 antibodies, and whether these antibodies are neutralizing.

10.2.1.3. Pharmacokinetic Evaluations

Concentration of the antibody-drug conjugate (ADC), total antibody and free MMAE will be determined using GLP compliant ELISA and LC-MS/MS methods. Population PK analyses will be performed to obtain pharmacokinetic parameters and to explore the relationships between patient-specific measures of exposure and safety and activity parameters; the influence of key intrinsic factors, such as weight and gender, on variability in PK will also be evaluated. The impact of circulating GPNMB levels on pharmacokinetic parameters may also be examined.

10.2.1.4. Pharmacodynamics

Pharmacodynamics will be evaluated via assessment of tumor tissue obtained via voluntary biopsy or re-resection. Parameters evaluated may include localization of CDX-011, CR011 or MMAE at the tumor site and/or GPNMB expression levels in tumor tissue, as well evaluation of tumor infiltrating leukocytes. Soluble GPNMB levels in circulation may also be examined.

10.2.2. Safety Variables

10.2.2.1. Adverse Events: Definition

An adverse event is any untoward medical occurrence in a patient administered a study treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. All observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be reported as described in the following sections. For the purposes of this current study, "study treatment" is defined as either CDX-011 or capecitabine.

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

- The appropriate descriptive term: Adverse events should be reported using concise medical terminology, preferably referring to the syndrome/diagnosis rather than symptoms, when possible.
- Severity: adverse event severity will be primarily assessed using NCI Common Terminology Criteria for Adverse Events v4.0. (CTCAE), Version 4.0, division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institute of Health (NIH), Department of Health and Human Services (DHHS) published May 29, 2009 at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- Onset/resolution dates and outcome
- Causality: the relationship of each adverse event to study drug will be defined as "unrelated" or "related" to study treatment:
    - Unrelated: There is little or no possibility that the study drug caused the reported adverse event; and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications appear to explain the adverse event.
    - Related: there exists at least a reasonable possibility that the study treatments caused or contributed to the adverse event; an inability to identify an alternate etiology for an adverse event should not, by itself, justify a "related" attribution.

- Whether it meets the criteria for classification as a serious adverse event (see **Section 10.2.2.2**).

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

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

10.2.2.2. Serious Adverse Events (SAEs): Definition

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

- Death (any AE that has a fatal outcome must be assigned CTCAE v. 4.0 Grade 5.)
- Requires initial or prolonged inpatient hospitalization (Any initial admission, even if less than 24 hours, to a healthcare facility meets these criteria. As well, any event occurring while the patient is hospitalized which would otherwise require hospitalization or requires transfer within the hospital to an acute/intensive care unit should also be reported under this criterion. This criterion would exclude hospitalization in the absence of a precipitating adverse event, such as admission for treatment of a preexisting condition not associated with a new/worsening adverse event, or admission for elective surgery. As well, admission to

rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries are not considered "hospitalizations" for the purpose of this criterion.)

- Is life-threatening (that is, immediate risk of dying)
- Is a persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other significant medical hazard (Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

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

- Progression of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for a serious adverse event. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an adverse event or serious adverse event as appropriate. Death due to disease progression occurring within 28 days of study treatment should be reported to Celldex within 24 hours of the site's awareness of the event; however, these events should not be documented as AEs or SAEs. If there is any uncertainty about the cause of death, the event should be reported as a serious adverse event.
- The following, although not necessarily meeting criteria for an SAE, should also be reported to Celldex Therapeutics, Inc. (or designee) according to SAE reporting processes:
    - If a female becomes, or is found to be, pregnant within 6 months of exposure to the study treatments (maternal exposure) or if a male has been exposed to the study treatments within 6 months prior to conception (paternal exposure).
    - Any follow-up to the above-referenced events, including outcome of pregnancy. Further follow-up of birth outcomes will be handled on a case-by-case basis. In the case of paternal exposure, the investigator must obtain permission from the subject's partner in order to conduct any follow-up or collect any information.

10.2.2.3. AE/SAE Reporting

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

Adverse Events (AEs) and Serious Adverse Events (SAEs) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment (CDX-011 or capecitabine) through (whichever occurs first) either a) 28 calendar days after the last administration of study treatment, or b) initiation of alternate anticancer therapy.

However:

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

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

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

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

10.2.2.4. Laboratory Safety Data

The following clinical laboratory tests will be performed during this study to assess safety (see Schedule of Assessments **Table 1** for specific tests):

- Hematology
- Serum Chemistries
- Urinalysis

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

10.2.2.5. Other Safety Data

The following evaluations will also be performed during the study to measure the safety and tolerability of CDX-011 and capecitabine chemotherapy:

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

11. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An independent data monitoring committee will review cumulative data on an interim basis. The interim data reviews may include but are not limited to summaries of adverse events, laboratory

values and vital signs. The IDMC will conduct reviews approximately every 6 months, or as frequently as deemed necessary by the IDMC, starting from the first randomized patient. If a safety concern is identified, the IDMC may recommend modifying, halting or permanently stopping the trial at any time. Further details will be described in the IDMC Charter.

12. STATISTICAL CONSIDERATIONS

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

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

12.1. Analysis Endpoints

Primary

- Duration of progression-free survival (PFS)

Secondary

- Objective response rate (ORR)
- Duration of response (DOR)
- Overall survival (OS)

Safety

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

12.2. Sample Size and Power Calculation

The primary efficacy endpoint will be PFS. For patients with metastatic advanced GPNMB-expressing breast cancer in the treatment setting under investigation, median PFS of 4 months is anticipated following randomization to capecitabine. It is hypothesized that CDX-011 will increase median PFS in such patients by 2.25 months (i.e., 4.0 vs 6.25 months). Under the assumption of proportional hazards, such an increase corresponds to a hypothesized hazard ratio of 0.64. If this hypothesized hazard ratio is true, 203 PFS events (total of two arms) determined by IRC will provide 85% power with 2-sided type I error of 0.05. Under the assumption of exponential distribution for each arm and uniform enrollment over 2 years, and 10% drop out rate (PFS events cannot be observed), 300 patients (200 in the CDX-011 arm and 100 in the capecitabine arm) are needed, and it is anticipated that 203 PFS events will be observed in

approximately 26 months from the date the first patient is randomized. The sample size calculation is performed using SAS v9.4.

12.3. Interim Analysis

There will be no interim analysis of efficacy in this study.

[Interim Analysis deleted]

12.4. Analysis Populations

12.4.1. Efficacy Analysis

The Intention-to-Treat (ITT) population will be the basis for the primary analysis of efficacy in this study, and constitutes all randomized patients. Patients in the ITT population will be included in the treatment arm to which they are randomized. Every effort will be made to ascertain outcomes for all randomized patients, irrespective of early discontinuation of protocol therapy.

A supportive analysis using the Per-Protocol population may be performed for the efficacy analysis. The Per-Protocol population excludes patients due to important deviations from the protocol that may substantially affect the results of the primary analysis. In addition, a baseline measurement and at least one follow-up measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific efficacy parameter. The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memo. Patients in the Per-Protocol population will be included in the treatment arm to which they are randomized.

12.4.2. Safety Analysis

The safety population will include all patients who receive at least one dose of study treatment (either CDX-011 or capecitabine). A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific safety parameter.

12.5. Statistical Methods

12.5.1. Efficacy Analysis

Progression-free survival

PFS is defined as the number of months from randomization to the earlier of disease progression or death due to any cause. The primary analysis of PFS will be based on PFS events determined by the IRC according to RECIST 1.1 (Eisenhauer, Therasse et al. 2009). Patients whom enter hospice care, or other such similar care, without prior objective evidence of disease progression will be considered to have disease progression for purposes of the primary analysis of PFS. Unless specified otherwise, all recorded PFS events will be included in the primary analysis regardless of stopping randomized therapy. Patients who initiate alternate anticancer therapy in the absence of documented progression will be censored at the latest disease assessment prior to initiation of such therapy. Patients who were last known to be alive and progression-free will be censored at the latest disease assessment. Patients with no baseline or post-baseline disease assessments will be censored at the randomization date unless death occurred prior to the first planned assessment (in which case the death will be considered a PFS event). A secondary analysis of PFS will be

performed based on PFS events determined by the local investigator. PFS will be summarized descriptively using the Kaplan-Meier method. The primary inferential comparison between treatment arms will use the log-rank test stratified by the randomization stratification factors. The hazard ratio for treatment will be estimated using a stratified Cox proportional hazards model.

Objective response rate

ORR is defined as the proportion of patients who achieve a best overall response of complete or partial response according to RECIST 1.1. The primary analysis of ORR will be based upon evaluations by the IRC. Inferential comparisons between treatment arms will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors.

Duration of objective response

DOR is defined as the number of months from the time criteria are first met for either CR or PR, until the first date that PD is objectively documented. Patients without documented disease progression will be handled as described above for the PFS analysis. The duration of objective response will be summarized descriptively using the Kaplan-Meier method. Inferential testing of DOR is not planned.

Overall survival

OS is defined as the number of months from randomization to the date of death due to any cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact. OS will be summarized descriptively using the Kaplan-Meier method. Inferential comparisons between treatment arms will use the stratified log-rank test. Stratification will be based on the stratification factors used for the randomization. The hazard ratio for treatment will be estimated using a stratified Cox proportional hazards model.

12.5.2. Protocol Therapy and Concomitant Medications

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

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

12.5.3. Safety Analysis

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

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing one or more AEs will be summarized by treatment arm, relationship to study drug, and severity. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline, and data listings of clinically significant abnormalities. Treatment-emergent AEs are defined as AEs that start on or after the first day study drug is administered. AEs will be summarized by the number and percentage of patients who experienced the event, according to system organ class and preferred term. A patient reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term. Unless specified otherwise, the denominator for these calculations will be based on the number of patients in each

treatment arm who receive at least one (1) dose of study drug, irrespective of the total number of doses administered. AEs will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. Additional summaries may also be provided for SAEs and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual patient data listings.

Vital sign results (systolic and diastolic blood pressure, pulse, respiration, and temperature) and ECG parameters will be summarized descriptively. Changes will be calculated relative to the assessments at baseline.

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

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Quality Assurance

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

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

Celldex (or designee) will provide Case Report Forms (CRFs) for the recording and collection of data. The CRF will either be in paper or via an electronic data capture (EDC) system. Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. Corrections to CRFs and source data will be made only by authorized members of the study staff, clearly entered, initialed and dated. The investigator will sign the CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will be made aware of the corrections and his/her approval will be documented by re-signing. In cases where an EDC system is utilized, an electronic audit trail is maintained with similar information collected.

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

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

13.2. Archiving of Study Documentation

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

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

14. ETHICAL CONSIDERATIONS

14.1. Independent Ethics Committee or Institutional Review Board

ICH GCP guidelines require that all investigational drug studies be conducted under the auspices of an IRB/EC. This committee, the makeup of which must conform to federal, state, and local guidelines regarding such, will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent. The investigator will provide Celldex (or designee) with a copy of the communication from the IRB/EC to the investigator indicating approval/favorable opinion of the protocol and consent form. All changes to the protocol or consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients.

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

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

14.2. Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The

study will also be carried out in keeping with applicable local law(s) and regulation(s). The investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

14.3. Patient Information and Informed Consent

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

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

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

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

14.4. Protocol Amendments

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

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

14.5. Confidentiality

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

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

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

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

15. PUBLICATION POLICY

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

Celldex encourages publication of the results of this trial in appropriate scientific journals and meetings. In accord with standard editorial and ethical practice, Celldex will generally support publication of multicenter trials only in their entirety and not as individual center data. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate Celldex personnel. Authorship will be determined by mutual agreement according to overall contribution to study conduct, chiefly by leadership in study design and decision making, and then by contribution, based upon enrollment to study.

Celldex must receive copies of any intended communication in advance of submission. Celldex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, provide any relevant supplementary information and protect proprietary information.

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Appendix 1: Approval Signature

Approval Signatures
Protocol CDX011-04

Celldex Therapeutics, Inc. Representative

28 July 2015
Date

Appendix 2: Investigator Signature

Investigator Signature

Protocol CDX011-04

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

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

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

Appendix 3: RECIST 1.1 Criteria

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

Only patients with measurable disease on baseline evaluations should be included in Protocol CDX011-04. (Measurable disease is defined by the presence of at least one measurable lesion; see "Measurability of Tumor at Baseline" below.) At baseline, lesions should be identified as either "Target" or "Non-Target" as follows:

Target Lesions:

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

Non-Target Lesions:

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

MEASURABILITY OF TUMOR AT BASELINE

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

  Note: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (for lymph nodes, only the short axis is measured and followed).

- Non-measurable: All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

- Malignant lymph nodes: Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. At baseline and in follow-up, only the short axis will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

- Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

- Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS OF LESION MEASUREMENT

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

- **TUMOR RESPONSE EVALUATION**

Evaluation of target lesions:

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

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

Special notes on the assessment of target lesions

- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.
- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion

sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions:

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

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

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

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

New lesions:

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

- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. (A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.)
    b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of overall response:

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

Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, **Table 2** is to be used.

Special notes on evaluation of overall response:

- Missing assessments and inevaluable designation:
    - When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

- If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

- 'Symptomatic deterioration': Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table 1** and **Table 2**.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.
- Confirmation of response: In the event of complete or partial responses, efforts should be made to obtain a confirmatory scan (no sooner than 28 days later).

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

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

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

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

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

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

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

FREQUENTLY ASKED QUESTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What may be done in such cases is one of the following:
(a) If the patient is still being treated, call the center to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable
(b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability
(c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel.
It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response.

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

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

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

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

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

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

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

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

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

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

Can PET–CT be used with RECIST?

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

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

Appendix 4: ECOG Performance Status

ECOG PERFORMANCE STATUS*

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

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

Appendix 5: Cockcroft and Gault Equation

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

Creatinine clearance for females = 0.85 x male value

Appendix 6: EORTC QLQ-C30 Questionnaire

Protocol CDX011-04: A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, GPNMB Over-Expressing, Triple-Negative Breast Cancer	Patient ID:
	Visit:

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Protocol CDX011-04: A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, GPNMB Over-Expressing, Triple-Negative Breast Cancer	Patient ID:
	Visit:

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7: Summary of Changes

The following changes have been made to protocol CDX011-04 as Amendment 4:

SECTION(S)	CHANGE/RATIONALE
3. Protocol Synopsis, Number of Study Centers	Increased maximum number of study centers from 150 to 175 due to anticipated expansion in the EU.
3. Protocol Synopsis, Eligibility Criteria 4, Schedule of Assessments, Table 1, Footnotes 9, 11 7.2.2. Subject Eligibility	In inclusion criteria 3 and 4 and Table 1 footnotes 9 and 11, deleted "locally advanced/recurrent/metastatic" which are examples of advanced disease settings but are not intended to be strict criteria. The following statement was inserted based on the [redacted] recommendation following the change to Inclusion Criterion 4 in Amendment 3: *"Patients with low hormone receptor expression (ER and/or PR 1-9%) must be deemed appropriate candidates for cytotoxic chemotherapy by the investigator."* For safety considerations added exclusion criterion 10: "*Previously received capecitabine and discontinued due to progressive disease or intolerance; previously received CDX-011 (CR011-vcMMAE; glematumumab vedotin) or other MMAE-containing agents.*" The original exclusion criterion 10 was deleted in amendment 2. For safety considerations added exclusion criterion 11: "*Active systemic infection requiring treatment. Infection controlled by oral therapy will not be exclusionary. Note: microscopic examination of urinalysis is required during screening. If urinary infection is suspected, then a negative urine culture is required prior to enrollment.*" The original exclusion criterion 11 was deleted in amendment 2. For safety considerations added exclusion criterion 12: "*Chronic use of systemic corticosteroid above the physiologic dose (5 mg per day prednisone or equivalent) within 7 days of enrollment, except for premedication.*" The original exclusion criterion 12 was deleted in amendment 2.
4. Schedule of Assessments Table 1	Added hematology and Adverse event monitoring to Cycle 1/Day 7 and Cycle 1/Day 14 as safety measures. To minimize study burden, noted in Footnote 29 that adverse event monitoring on Cycle 1/Day 7 and Cycle 1/Day 14 could be performed in person or by telephone call, thereby moving original text in Footnote 29 to new Footnote 30. Shortened visit window of Cycle 2/Day 1 from +/-5 days to +/-3 days. Footnote 17. For consistency with exclusion criterion 11, added the requirements of microscopic examination of urinalysis at baseline and negative urine culture prior to enrollment if urinary infection is suspected. Footnote 21. Increased the number of patients for PBMC collection from the first 80 patients to up to 150 patients enrolled at a subset of study centers. The increase is to ensure that an adequate number of patients can provide samples from 3 time points (Cycle 1/Day 1, Cycle 2/Day 1, and End of Treatment) in order to generate sufficient and meaningful data. The following statement was also added: *"Celldex will notify the sites when the requisite number of patients providing PBMC samples has been reached or that further data is not needed."* Footnote 28. Clarified that rash biopsies are only encouraged from patients who received CDX-011 by changing "treatment-related rash" to "rash possibly related to CDX-011."

5.4. CDX-011	Added references for the CR011-CLN-11, CR011-CLN-20, and CDX011-03 studies. Table 4. Updated table with final results from the CDX011-03 study.
8.1.7.2. Management of Toxicity	A section has been added on "Infections and Sepsis" as potential and previously observed toxicities of glembatumumab vedotin. Additional information has been included on the signs and management of infection.
9. Concomitant Therapy	For safety considerations added that prolonged use of systemic corticosteroids above the physiologic dose (5 mg prednisone or equivalent) should be avoided during the study.
Synopsis, Overview of Study Design, Statistical Methods 11. Independent Data Monitoring Committee (IDMC) 12. Statistical Considerations, 12.3 Interim Analysis	The following statements were deleted based on the [redacted] recommendation to remove the interim analysis of PFS: *"In addition, an interim analysis of PFS will occur at 102 PFS events (50% information). The study may be stopped early if the futility boundary for PFS is met."* *"…for a group sequential design with one interim analysis planned at 50% of target PFS events (102) using O'Brien Fleming alpha spending boundary."* *"At the time of the interim analysis, futility will also be considered with the non-binding futility boundary for PFS defined as the observed hazard ration (HR)≥0.90. The study may be stopped early if the futility boundary for PFS is met. The interim analysis will be performed by an independent statistical services provider in conjunction with the IDMC."* *"The DMC will provide recommendations about stopping or continuing the trial based on the interim analysis…"* The following section was deleted in its entirety: Section 12.3 Interim Analysis. Consequently, sample size calculations now require only 203 events (rather than 204 events) for PFS analysis and this change is reflected in the protocol.
12. Statistical Considerations, 12.5.1 Efficacy Analysis	The statement referring to the sensitivity analysis and associated references were removed as the scope of the sensitivity analysis will be specified in the Statistical Analysis Plan.
Throughout	Formatting adjustments and typographical corrections

The following changes have been made to protocol CDX011-04 as Amendment 3:

SECTION(S)	CHANGE/RATIONALE
Synopsis, Indication and Eligibility Criteria 5.5. Study Rationale 7.2.2.1. Inclusion Criteria 7.2.2.2. Exclusion Criteria	To facilitate accrual, the study population is now described as, *"Patients with metastatic, GPNMB over-expressing, triple-negative breast cancer, who have failed taxane therapy and who have received anthracycline therapy or for whom anthracycline therapy is not clinically indicated."* The following eligibility criteria have also been revised accordingly: • Inclusion criterion 4: Minimal or no expression of estrogen and progesterone receptors will be defined by <10% of cells positive by IHC (rather than <1%), consistent with current acceptable standards of care. • Inclusion criteria 6 and 7: The eligibility restrictions requiring "resistance" to anthracycline and taxane therapy have been removed. These eligibility criteria now read,

SECTION(S)	CHANGE/RATIONALE
	6. *Prior receipt of anthracycline-containing chemotherapy in any setting, unless anthracycline therapy is not clinically indicated, in the opinion of the treating investigator* ***7.*** *Prior receipt of taxane-containing chemotherapy, in any setting* • Exclusion criterion 1: The required progression-free interval following neo/adjuvant therapy has been reduced from 6 months to 3 months
Synopsis, Overview of study design 7.1. Overall Design and Plan of the Study	In accordance with the above changes to the patient population, stratification factors have been changed from: • *"Resistant" to anthracycline therapy (i.e., progression-free interval of ≤ 6 months after completing treatment) vs. "Exposed" to anthracycline therapy (i.e., progression-free interval of > 6 months after completing treatment).* to: • *Progression-free interval ≤ 6 months after receipt of taxane therapy vs. progression-free interval > 6 months after receipt of taxane therapy* • *Received anthracycline therapy previously vs. no prior anthracycline therapy*
Synopsis, Objectives, Overview of study design, Criteria for Evaluation, and Statistical Methods 6. Study Objectives 7.1. Overall Design and Plan of the Study 10.2.1.1. Anti-tumor Activity 12.1. Analysis Endpoints 12.2. Sample Size and Power Calculation 12.3. Interim Analysis 12.5.1. Efficacy Analysis	The primary endpoint of the study has been changed to Progression-Free Survival only, with Objective Response Rate now included as a secondary endpoint. The statistical section has therefore been revised as followed: • Sample size calculation is modified based on the primary endpoint of PFS with 85% power and 2-sided 5% type I error. The number of subjects (300) remains the same, but the target number of PFS events at final analysis is modified to 204. • Interim analysis will be based on PFS (not ORR), and will include superiority and futility considerations. The timing of the interim analysis is determined as 50% PFS events. • OS, as a secondary endpoint, will be analyzed at the interim and final analyses to support PFS and to demonstrate no detrimental effect on survival. After final analysis of PFS, patients will continue to be followed for survival and updated OS analysis maybe performed as events accumulate.
7.2.5. Completion of Study	The enrollment period is updated from 1.5 years to 2 years.
Throughout	Minor formatting and typographical changes.

The following changes have been made to protocol CDX011-04 as Amendment 2.1:

SECTION(S)	CHANGE/RATIONALE
Synopsis, Eligibility Criteria 7.2.2. Subject Eligibility	Exclusion #9 has been revised to reflect that the requirement for use of effective contraception also applies to men enrolled in the study.

SECTION(S)	CHANGE/RATIONALE
10.2.2.2. Serious Adverse Events (SAEs): Definition	Requirements for reporting of pregnancy have been revised to include reporting of cases in which a male has been exposed to the study treatments within 6 months prior to conception (paternal exposure).

The following changes have been made to protocol CDX011-04 as Amendment 2:

SECTION(S)	CHANGE/RATIONALE
2. Glossary of Abbreviations	Abbreviations re-ordered and updated.
Synopsis, Overview of study design 7.1. Overall Design and Plan of the Study	Stratification factor, "No prior chemotherapy for advanced disease vs. 1 prior line of chemotherapy for advanced disease" has been changed to "0-1 prior line of chemotherapy for advanced disease vs. 2 prior lines of chemotherapy for advanced disease", for consistency with revised eligibility criteria.
Synopsis, Eligibility Criteria 7.2.2. Subject Eligibility	Inclusion #1: Revised to allow for inclusion of male subjects, in accordance with [redacted] suggestion. Inclusion #2: Further clarity regarding the definition of documented progression of disease prior to study entry is provided; "…based on radiographic, clinical or pathologic assessment showing increased tumor burden or new site(s) of disease during or subsequent to the last anticancer regimen received." Inclusion #3: Further clarity regarding definition for gpNMB expression is re-inserted; "≥ 25% of malignant epithelial cells expressing GPNMB, as determined by a central laboratory using IHC methods." Inclusion #4: Revised to allow for local determination of TNBC status, in order to facilitate patient accrual and simplify study conduct. Clarification added that laboratory reports will be required to provide quantitative results of sufficient detail to verify eligibility for all patients enrolled. Definition for HER2-negative status is also updated in accordance with recently revised ASCO/CAP guidance (Wolff, Hammond et al. 2014). Inclusion #5: To facilitate accrual, the eligibility criteria have been revised to allow for 0-2 (rather than 0-1) prior chemotherapy-containing regimens for advanced breast cancer. Inclusion #7: Revised to allow for inclusion of patients for whom no further taxane therapy is indicated, due to treatment-limiting toxicity to prior taxane therapy (received in any setting) or persistent comorbidities that contraindicate further therapy, in the opinion of the treating investigator. Exclusion #7: Revised to clarify that, "Continued use of steroids and/or anticonvulsants (in the absence of any suspicion for progressive brain metastases) is acceptable." Exclusion #9: Detailed examples of "effective contraception" are provided as, "…double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, contraceptive sponge, vaginal ring or intrauterine device), intra-uterine device (IUD), implants, injectables, combined oral contraceptives, sexual abstinence (total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable), or sexual intercourse with only a vasectomized partner. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement." With consideration to [redacted] feedback indicating that no further QT studies are required with CDX-011, the following exclusion criteria have been deleted

SECTION(S)	CHANGE/RATIONALE
	"10. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms). 11. A history of additional risk factors for torsades de pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome). 12. The use of concomitant medications that prolong the QT/QTc interval (Appendix 6)." Appendix 6 also removed accordingly.
4. Schedule of Assessments	Visit windows updated to allow for up to 5 day delay in initiation of capecitabine cycles, consistent with standard of care. Randomization added to screening visit (along with footnote #25, as noted below). Footnote #1: Added to facilitate study conduct, "A delay in study treatment or performance of study visits due to holidays, weekends, inclement weather or other unforeseen circumstances will be permitted and not considered a protocol violation. However, significant delays (i.e., greater than one week) should be discussed with the study medical monitor to reach consensus on subsequent scheduling." Footnote #6 (now #7): ECG, pregnancy test and EORTC QLQ-C30 are added to assessments that are not required to be repeated if performed at screening within 24 hours of Cycle 1, Day 1. Footnote #7 (now #8): Revised for consistency with inclusion criterion #3 and 4, "Assessment of GPNMB expression (by IHC) will be performed at a central laboratory…Additional analyses to be performed centrally may also include…" Footnote #11: Added for consistency with inclusion criterion #4, "Determination of triple-negative status will be done at a local laboratory. Tumor sample(s) used to determine eligibility must be obtained in the setting of advanced (locally advanced, recurrent or metastatic) disease. Laboratory reports will be required to provide quantitative results of sufficient detail to verify eligibility for all patients enrolled (see study entry criteria)." Footnote #15 (now #17): Clarification added, "Differential should be reported consistently throughout the study as either an absolute count (preferred) or as a percentage." Footnote #20 (now #22): Text clarified to note that the mutation/molecular analyses will be performed retrospectively. Footnote #25: Added for clarity, "Randomization may be performed up to 5 days prior to initiation of study treatment, but should occur only after confirming all eligibility criteria have been met." Footnote #23 (now #26): Revised to allow for study assessments to be performed within 24 hours prior to day 1 of each treatment cycle, provided that assessments remain within the specified visit window. Footnote #28: Added to allow for further evaluation of treatment-related rash: "For patients who develop grade 3 treatment-related rash and who provide appropriate consent, punch biopsies and photographs of the rash site, as well as uninvolved skin, are strongly encouraged. Samples may be submitted for central analyses including quantification of gpNMB expression; in these cases, collection, processing and shipping instructions will be provided separately."
5.4. CDX-011	Language clarified to reflect that updates to data relative to the investigation will be provided as revisions to the Investigator's Brochure and through IND Safety Reports submitted to the Investigator by Celldex rather than by amendment to this section of the protocol.

SECTION(S)	CHANGE/RATIONALE
8.1.5. Preparation and Administration 9. Concomitant Therapy	Clarification added; growth factor support should be administered with consideration to the American Society of Clinical Oncology (ASCO) guideline on the use of hematopoietic colony-stimulating factors (Smith, Khatcheressian et al. 2006).
8.1.7.2. Management of Toxicity (Dermatologic Toxicities)	Added to allow for further evaluation of treatment-related rash: Sites are encouraged to collect photographic records of rashes for the medical record and dermatological consults as needed. Skin biopsy collection and assessment of histology by a local pathology lab is strongly encouraged, as is quantitation of gpNMB by the central laboratory (see Table 1, Footnote 26).
8.2.1. Description, Packaging, Labeling, Accountability and Storage	Reference to trade name and manufacturer for capecitabine deleted; added clarification that generic capecitabine may be utilized.
8.2.3. Administration 8.2.4. Dose Modifications	Language added to clarify that investigators are encouraged to follow the recommended dosing from the Capecitabine Package Insert and NCCN Guidelines (available on-line at www.nccn.org), as well as institutional standard and that management of capecitabine toxicity, dosing, dose reductions and supportive care should be consistent with the package insert recommendations, but should be dictated by institutional and Investigator standard practice and the need for individual patient management.
12. Statistical Considerations	Clarifying language added, "Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by Celldex (or designee). This documentation may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment."
13.1. Data Quality Assurance	Language revised for consistency with use of eDC system.
14.4. Protocol Amendments	Text edits for consistency with current template language. Any amendments to, or deviations from, the protocol to eliminate an immediate hazard(s) to the trial patient(s) should be submitted to the IRB as soon as practical. Eligibility waivers are not encouraged.
Throughout	References to CTCAE have been completed with v. 4.0. Miscellaneous formatting, typographical corrections, and minor text edits for consistency with current Celldex template language.

The following changes have been made to protocol CDX011-04 as Amendment 1:

SECTION(S)	CHANGE/RATIONALE
Synopsis, Indication 5.5. Study Rationale	Study eligibility have been revised to ensure that enrolled patients are taxane-resistant; as such, the indication is now described as, "Patients with metastatic, GPNMB over-expressing, triple-negative breast cancer, who are taxane-resistant and have received an anthracycline-containing chemotherapy regimen."

SECTION(S)	CHANGE/RATIONALE
Synopsis, Overview of Study Design 7.1. Overall Design and Plan of the Study	As all enrolled patients will now be taxane-resistant, enrollment will be stratified by whether patients are exposed or resistant to anthracycline only.
Synopsis, Eligibility Criteria 7.2.2.1. Inclusion Criteria	Inclusion #2 added to ensure enrollment of patients with progressive disease; *"Documented progression of disease after last anticancer regimen."* Inclusion #2 (now #3): Revised to exclude details regarding IHC for GPNMB. Assay methodology will be included in separate study-specific documentation. Inclusion #4 (now #5): wording change for clarity. Criterion changed from, *"**No more than one** chemotherapy-containing regimen…"* now reads, *"**0 or 1 prior** chemotherapy-containing regimen for advanced (locally advanced, recurrent or metastatic) breast cancer."* Inclusion #5 (now #6 and #7): revised to require taxane resistance and further clarify acceptable situations where additional anthracycline therapy would not be required for patients who have not received cumulative doses of 240 mg/m^2: *6. Prior receipt of anthracycline-containing chemotherapy in any setting.* *a. If received as neoadjuvant/adjuvant therapy, there must have been a progression-free interval of > 6 months after completion of neoadjuvant/adjuvant therapy and no further anthracycline therapy should be indicated.** *b. If received in the setting of advanced (locally advanced, recurrent or metastatic) disease, there are no restrictions based on the subsequent progression-free interval; however, any patient who had a progression-free interval of > 6 months after completion of advanced disease therapy should have no further anthracycline therapy indicated.** ** Patients in whom no further anthracycline therapy would be indicated include those with contraindicating cardiac conditions, prior intolerance to anthracycline therapy, or those who have received cumulative doses of 240 mg/m^2 of doxorubicin or doxorubicin equivalents.* *7. Taxane resistance, defined by at least one of the following:* *a. If received in the neoadjuvant/adjuvant setting, there must have been a progression-free interval of > 6 months after completion of neo/adjuvant therapy. Furthermore, if the progression-free interval was >12 months after completion of neo/adjuvant therapy, the patient must have received additional taxane-containing therapy (i.e., a taxane re-challenge) for advanced disease and had progression while receiving or within 6 months of completing the taxane-rechallenge therapy.* *b. If received in the setting of advanced (locally advanced, recurrent or metastatic) disease, there must have been progression while receiving or within 6 months of completing advanced disease therapy.* Inclusion #9 (now #11): Revised to remove inaccurate definition of target disease per RECIST 1.1. Now reads, "*Measurable (target) disease by RECIST 1.1 criteria (Eisenhauer, Therasse et al. 2009) (Appendix 3). Target lesions selected for tumor measurements should be those where surgical resection or radiation are not indicated or anticipated.* Inclusion #14 (now #16): Revised to include "if applicable" relative to HIPAA, as HIPAA is not applicable in countries planed for participation.
Table 1. Schedule of Assessments 10.1.1. Screening Period	Consistent with the change to eligibility, "if applicable" has been inserted relative to HIPAA.

SECTION(S)	CHANGE/RATIONALE
Table 1. Schedule of Assessments	Footnote #6 (stating that the assessments does not need to be repeated if completed within the previous 24 hours as part of screening) has been applied to the Cycle 1/Day 1 urinalysis. "BRCA mutation analysis" has been changed to "Molecular profiling" and footnote #20 has been revised to more accurately describe the planned analyses; *"Blood sample for BRCA1/2 mutation status and other potentially relevant molecular markers."* Footnote #4: Frequency of survival follow-up for patients who discontinue study treatment in the absence of progression has been amended 6 (±1) or 9 (±2) weeks, consistent with Disease Assessment Visits. Footnote #8: wording corrected to specify that tissue for screening GPNMB analysis must have been obtained in the advanced disease (locally advanced, recurrent or metastatic) setting, rather than only in the metastatic setting, consistent with eligibility. Footnote #18: wording revised to specify that "other soluble mediators" may be examined in serum samples. Footnote #22: revised to reference the applicable Site Manual that will be provided by Celldex (or designee), and further clarify expected methodology for tumor evaluation as follows, *"Contrast-enhanced CT of the chest, abdomen, and pelvis, as well as all other suspected disease sites is required. MRI exams of the brain, abdomen, and pelvis can be performed in lieu of a CT; however MRI exams of the chest are not recommended. In the event that a chest MRI is performed, a non-contrast chest CT is strongly recommended to evaluate the lung parenchyma. Brain and/or bone scans are required for any patients with a history of metastases to bone and/or brain or where symptomatology raises the suspicion for bone and/or brain metastases. Lesions identified on bone scans should be confirmed by a CT or MRI at baseline, and, if identified as target lesions due to soft tissue component, they should continue to be followed by the same methodology (i.e., CT or MRI scan). However, bone lesions followed as non-target disease may be subsequently followed by bone scans only. Lesions that cannot be imaged but are assessable by clinical exam may be assessed using color photography including a ruler (preferred method) or measured with calipers."*
Table 1. Schedule of Assessments 8. Concomitant Medications	Footnote #24: reporting of concomitant medications revised for consistency with safety follow-up, *"…concomitant medications required to treat CDX-011-related SAEs taken throughout the duration of study follow-up should also be recorded."*
8.1.6. Dose Modifications	Further detail provided regarding the management of neuropathy, as follows, *"Patients that develop Grade 2 or 3 neuropathy will have dosing held until neuropathy improves to Grade 1 or baseline, and will be restarted with a dose reduction. Patients with Grade 4 neuropathy should have treatment discontinued altogether."*
8.1.7.2. Management of Toxicity	Cross-reference added to Section 8.1.6 for management of neuropathy.
8.2.4. Dose Modifications	Word changed to encourage prompt modification of capecitabine dose in the event of toxicity, to avoid attrition due to toxicity in the control arm.
10.2.2.3. AE/SAE Reporting	Wording changed to clarify follow-up period for ongoing, treatment-related adverse events, "For AEs or SAEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve to ≤ Grade 1, or stabilize for at least three months after the last administration of study treatment (whichever is sooner)."
Throughout	Miscellaneous formatting and typographical corrections.