2 SYNOPSIS

Name of Sponsor/Company: Celldex Therapeutics, Inc. **Name of Test Drug:** Glembatumumab vedotin **Name of Active Ingredient:** Glembatumumab vedotin	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Study Title: A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, gpNMB-Overexpressing, Triple-Negative Breast Cancer (The "METRIC" Study) (CDX011-04)		
Investigators/Centers/Countries: 172 sites were opened, 151 sites screened patients, and 120 study sites enrolled patients in the United States, Canada, Australia, Belgium, France, Germany, Italy, Spain, and United Kingdom.		
Studied Period: Date first subject dosed: 20 FEB 2014 Date last subject terminated: 07 AUG 2018		**Phase of Development:** 2b
Publications (reference): None		

Objectives:

The primary objective was:

- To evaluate the anticancer activity of glembatumumab vedotin in metastatic, gpNMB-overexpressing, triple-negative breast cancer (TNBC) as measured by the duration of progression-free survival (PFS)

The secondary objectives were:

- To further assess the anticancer activity of glembatumumab vedotin in metastatic, gpNMB-overexpressing, TNBC, as assessed by the objective response rate (ORR), duration of response (DOR), and overall survival (OS)
- To further characterize the safety of glembatumumab vedotin in metastatic, gpNMB overexpressing, TNBC
- To obtain pharmacokinetic parameters and to explore the relationships between patient-specific measures of exposure and safety and activity parameters

The exploratory objectives were:

- To assess whether treatment with glembatumumab vedotin is associated with improvements in quality of life and/or cancer-related pain as reflected by reduced analgesic use

Methodology:

The METRIC study was a pivotal, open-label, prospectively controlled, randomized study designed to demonstrate that glembatumumab vedotin improves PFS as compared to capecitabine in patients with gpNMB-overexpressing TNBC. The primary analysis of PFS was based on PFS events determined retrospectively by the central independent review committee (IRC), blinded to treatment assignment and investigator assessments, according to RECIST 1.1 criteria.

Eligible patients were stratified based on prior receipt of anthracycline, progression-free interval since last taxane treatment, and number of prior cytotoxic chemotherapies in the advanced disease setting. Patients were randomized 2:1 to receive glembatumumab vedotin or capecitabine until progression or intolerance.

Disease assessments were performed every 6 (±1) weeks for 6 months and every 9 (±2) weeks thereafter, until progression. Patients who discontinued study treatment without documented progression of disease as per RECIST 1.1 continued to have disease assessment visits until such criteria were met, regardless of intervening changes in therapy. Local investigator assessments guided individual treatment decisions.

Safety assessments occurring at every 21-day cycle included physical examination, vital signs, routine hematology, blood chemistry, urinalysis, and evaluation of adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0. The EORTC Core Quality of Life Questionnaire (QLQ-30) was completed at screening, at first dose of study drug, and at every other dosing cycle until the end of treatment by patients who were fluent in a language in which the questionnaires were validated.

An independent data monitoring committee (IDMC) was convened for this study and acted in an advisory capacity to the sponsor with respect to safeguarding the interests of patients, assessing interim safety data, and for monitoring the overall conduct of the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 300 subjects were to be enrolled

Analyzed: Overall 327 subjects were randomized to receive glembatumumab vedotin (N=218) or capecitabine (N=109) and were included in the ITT population. Of these, 305 patients (N=213 [65%] in the glembatumumab vedotin arm and 92 [28%] in the capecitabine arm) received study treatment and were included in the Safety population. Twenty-two (7%) patients were not treated.

Diagnosis and Main Criteria for Inclusion:

Males or females aged ≥ 18 years with gpNMB-overexpressing, metastatic TNBC, who had failed taxane therapy and had received anthracycline therapy, unless not clinically indicated, and who had received no more than 2 prior chemotherapy-containing regimens for advanced breast cancer. Overexpression of gpNMB was defined as ≥ 25% tumor epithelial cells staining positive for gpNMB in a sample obtained in the advanced disease setting as assessed by immunohistochemistry at a central laboratory, NeoGenomics Laboratories (formerly Clarient, Inc.), Aliso Viejo, CA. Triple-negative status was confirmed in the advanced disease setting and defined as follows:

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 to 9%) must have been 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[1] ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell).

Disease progression during or subsequent to the last anticancer regimen received must have been documented. Patients must have had ECOG performance status of 0-1, life expectancy ≥ 3 months, measurable (target) disease by RECIST 1.1 criteria, and adequate bone marrow, renal, and liver function. Persistent neuropathy grade ≥ 1, prior receipt of capecitabine (unless discontinued due to reasons other than progression or intolerance), and active systemic infections not controlled by oral

[1]Also referred to as CEN17.

therapy were exclusionary. All patients provided written informed consent. Full eligibility criteria can be found in the trial protocol.

Test Product, Dose and Mode of Administration, Batch Number(s):

Glembatumumab vedotin solution (injection concentrate); 1.88 mg/kg; intravenous infusion on Day 1 of repeated 21-day cycles. Lots used were 120044, 140042, and 150092.

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

Capecitabine administered orally; starting dose was 1,250 mg/m^2 twice daily (equivalent to 2,500 mg/m^2 total daily dose) per the package insert; days 1 to 14 of repeated 21-day cycles; subsequent treatment was dictated by tolerance and institutional practice. Capecitabine was supplied by Celldex in the EU with the exception of one site in France and seven sites in Germany that used their own commercial supply. Lots used in the EU were PS02202, PW01315, PS01182, PT00357, and PW01428. Sites in the USA, Canada, and Australia used their own commercial supply.

Duration of Treatment:

Glembatumumab vedotin and capecitabine were administered until disease progression or intolerance.

Criteria for Evaluation:

Efficacy:

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

Pharmacokinetics: Glembatumumab vedotin parameters and relationships between patient-specific measures of exposure and safety and activity parameters

Pharmacodynamics: Localization of glembatumumab vedotin, CR011, or MMAE at the tumors site and/or gpNMB expression in tumor tissue as well as evaluation of tumor infiltrating leukocytes; soluble gpNMB levels in circulation; gpNMB expression on myeloid cells in peripheral blood

Safety: Safety was assessed by the incidence and severity of treatment-emergent and treatment-related adverse events, serious adverse events, vital sign measurements, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, ECGs, and ECOG performance status

Immunogenicity: Humoral immune responses to glembatumumab vedotin

Quality of Life: EORTC QLQ-30 questionnaire and analgesic use for cancer-related pain

Statistical Methods:

The primary efficacy endpoint was PFS. For patients with metastatic advanced TNBC in the treatment setting under investigation, a median PFS of 4 months was anticipated following randomization to capecitabine. It was hypothesized that glembatumumab vedotin would 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 corresponded to a hypothesized hazard ratio of 0.64. If this hypothesized hazard ratio was true, 203 PFS events (total of two arms) determined by IRC would provide 85% power with 2-sided type I error of 0.05. Under the assumption of 10% drop out rate (PFS events cannot be observed), 300 patients (200 in the glembatumumab vedotin arm and 100 in the capecitabine arm) were needed. The sample size calculation was performed using SAS v9.4.

The analysis populations were as follows:

- Intention-to-Treat (ITT) population was the basis for the primary analysis of efficacy in this study and constituted all randomized patients. Patients in the ITT population were included in the treatment arm to which they were randomized.
- A supportive analysis using the Per-Protocol population was performed for the efficacy analysis. The Per-Protocol population excluded patients due to important deviations from the protocol that may substantially have affected the results of the primary analysis. The final determination on protocol violations, and thereby the composition of the Per-Protocol population, was made prior to locking the clinical database and final analysis and was documented in a separate memo. Patients in the Per-Protocol population were included in the treatment arm to which they were randomized.
- The safety population included all patients who received at least one dose of study treatment (either glembatumumab vedotin 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 was required for inclusion in the analysis of a specific safety parameter.

Efficacy was assessed as follows:

PFS was defined as the number of months from randomization until disease progression or death due to any cause. The primary analysis of PFS was based on PFS events determined by the IRC according to RECIST 1.1 (Eisenhauer, Therasse et al. 2009). Patients who initiated alternate anticancer therapy in the absence of documented progression were censored at the latest disease assessment prior to initiation of such therapy. Patients who were last known to be alive and progression-free were censored at the latest disease assessment. Patients with no baseline or post-baseline disease assessments were censored at the randomization date unless death occurred prior to the first planned assessment (in which case the death was considered a PFS event). A secondary analysis of PFS was performed based on PFS events determined by the local investigator. PFS was summarized descriptively using the Kaplan-Meier method. The primary inferential comparison between treatment arms used the log-rank test stratified by the actual stratification factors. The hazard ratio for treatment was estimated using a stratified Cox proportional hazards model.

ORR was defined as the proportion of patients with measurable disease at baseline who achieve a best overall response of complete or partial response according to RECIST 1.1. The primary analysis of ORR was based upon evaluations by the IRC. Inferential comparisons between treatment arms were made using the Cochran-Mantel Haenszel chi-square test, stratified by the actual stratification factors.

DOR was defined as the number of months from the time criteria are first met for either CR or PR, until the first date that PD was objectively documented. Patients without documented disease progression were handled as described above for the PFS analysis. The DOR was summarized descriptively using the Kaplan-Meier method.

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

There was no interim efficacy analysis in this study.

Summary tables and listings were provided for all reported treatment-emergent adverse events (TEAEs). Hematology, serum chemistry values, and vital signs (actual value and change from baseline value) as well as ECOG performance status scores were summarized by calculating the mean, standard deviation, median, and range by treatment arm. ECOG post-baseline scores were also summarized using the conventions described for laboratory values and vital signs. ECGs were summarized and descriptive statistics were tabulated for QT interval values. Physical examinations (whether performed or not and

date of exam) were provided in individual patient listings only. Deaths were reported in a patient listing format.

SUMMARY OF RESULTS

The primary analysis was performed using a clinical data cutoff of 30Nov2017. As the primary analysis did not demonstrate an improvement in PFS for glembatumumab vedotin as compared to capecitabine, the study was closed. Patients still in follow-up were seen for a final visit before removal from study while three patients continuing treatment with glembatumumab vedotin were offered the option to transition to compassionate use treatment. The last patient visit in METRIC occurred on 07AUG2018. Study analyses presented in this CSR are based on the cut-off date of 30Nov2017. However, select supplementary data are also provided, including a listing of SAEs occurring through the study closure date of 07AUG2018, and an updated analysis of OS with a clinical data cut-off date of 02APR2018, the date of the database lock for the primary analysis.

Study Population:

Between 19Feb2014 and 21Aug2017, 327 patients were randomized to receive glembatumumab vedotin (N=218) or capecitabine (N=109) and were included in the ITT population. Twenty-two patients were randomized but did not receive treatment, including 5 patients in the glembatumumab vedotin arm and 17 patients in the capecitabine arm. As of the clinical data cut-off date for primary analysis on 30Nov2017, 21 patients remained on treatment and 98 patients were being followed up for survival.

Pretreatment demographic, baseline, and disease characteristics were well balanced between treatment groups. Overall, the patient population was: 100% female; 82% white/Caucasian; median age = 55 years; 77% visceral disease; 3% current CNS involvement; 50% ≥ 3 sites of disease; 2.4 years median duration of disease at study entry; and 1 median prior anticancer regimen for advanced or metastatic disease.

Efficacy:

PFS did not differ significantly between the treatment arms. As of the clinical cut-off date for the primary analysis, a total of 223 progression events (154 in the glembatumumab vedotin arm and 69 in the capecitabine arm) had occurred according to IRC review. By IRC, median PFS for the glembatumumab vedotin and capecitabine arms, respectively, was 2.9 months (95% CI: 2.8, 3.5) and 2.8 months (95% CI: 1.6, 3.2) in the ITT population (HR = 0.95, $P = 0.76$), and was 3.0 months (95% CI: 2.8, 3.9) and 2.9 months (95% CI: 1.9, 3.4) in the per-protocol population (HR = 1.0, $P = 0.99$).

As of the clinical cut-off date for the primary analysis, a total of 244 progression events (173 in the glembatumumab vedotin arm and 71 in the capecitabine arm) had occurred according to investigator review. By investigator review, median PFS for the glembatumumab vedotin and capecitabine arms, respectively, was 2.9 months (95% CI: 2.8, 3.1) and 2.7 months (95% CI: 1.8, 3.4) in the ITT population (HR = 1.1, $P = 0.41$), and was 2.9 months (95% CI: 2.8, 3.5) and 2.9 months (95% CI: 1.9, 3.6) in the per-protocol population (HR = 1.2, $P = 0.18$).

There was no significant advantage for glembatumumab vedotin in the secondary endpoints (OS, ORR, DOR) or in any planned subgroups. OS in the ITT population was 8.9 months (95% CI: 7.9, 10.5) and 8.7 months (95% CI: 6.9, 10.8) in the glembatumumab vedotin and capecitabine arms, respectively. In an updated analysis with a later clinical data cut-off date of 02Apr2018, OS in the ITT population was 9.0 months (95% CI: 8.0, 10.4) in the glembatumumab vedotin arm and 8.7 months (95% CI: 7.3, 10.8) in the capecitabine arm. The ORR by IRC review in the measurable disease ITT population was 26% in the glembatumumab vedotin arm and 21% in the capecitabine arm ($P = 0.26$). DOR was 2.8 months (95% CI: 2.3, 5.5) and 4.2 months (95% CI: 2.7, 5.6) in the glembatumumab vedotin and capecitabine arms, respectively. In the glembatumumab vedotin arm, 1 (1%) patient and 45 (25%) patients

experienced a complete response and partial response, respectively. In the capecitabine arm, 3 (3%) patients and 18 (18%) patients experienced a complete response and a partial response, respectively.

A post hoc, retrospective subgroup analysis suggested potential benefit from glembatumumab vedotin in taxane-sensitive disease (i.e., not previously re-challenged or > 6 months progression-free interval following last taxane). For patients with 0 to 1 prior taxane therapies, the median PFS was 3.0 months in the glembatumumab vedotin arm and 1.9 months in the capecitabine arm (HR = 0.67, [95% CI: 0.47, 0.95], *P* = 0.02), while the Clinical Benefit Rate (CBR [best overall response=complete response/partial response/stable disease ≥ 24 weeks]) was 33% in the glembatumumab vedotin arm and 21% in the capecitabine arm (*P* = 0.04). For patients with a progression-free interval > 6 months after last taxane, the median PFS was 4.1 months in the glembatumumab vedotin arm and 2.7 months in the capecitabine arm (HR = 0.70, [95% CI: 0.46, 1.04], *P* = 0.0773), while the CBR at ≥ 24 weeks was 40% in the glembatumumab vedotin arm and 23% in the capecitabine arm (*P* = 0.0215).

Pharmacokinetics:

Samples were obtained from 201 patients and included pre and post-infusion samples in each cycle and at the end of treatment. A partial analysis provided mean TA, ADC, and MMAE concentrations. Mean post-infusion serum concentration of ADC in cycle 1 was 58.6 ± 15.5 μg/mL with mean TA at 49.4 ± 16.5 μg/mL (range: 21.4 to 127.4 μg/mL). In cycle 2, the mean post-infusion ADC concentration was 56.1 ± 11.0 μg/mL and for TA was 47.3 ± 15.0 μg/mL. Mean free MMAE concentration at the end of infusion at cycle 1 was 1.5 ± 1.1 ng/mL and at cycle 2 was 1.40 ng/mL post-infusion. Maximum concentrations of ADC and free MMAE did not seem to differ between patients when grouped by best overall response, although non-parametric comparisons did suggest a small significance in median peak TA levels (*P* = 0.048). Median cycle 1 TA levels appear higher in patients who experienced rash in cycle 1. Comparison of maximum cycle 1 concentrations of ADC, TA, and MMAE in subjects with TRAEs < grade 3 vs. levels in patients experiencing TRAEs ≥ grade 3 did not reveal any significant differences.

Pharmacodynamics:

Prior to study entry, all patients were required to have gpNMB overexpression, as defined by ≥ 25% of tumor cells expressing gpNMB according to central immunohistochemistry of a sample obtained in the advanced disease setting. Outcomes were analyzed for the subgroups with ≥ 25 to 50% and > 50% of tumor cells expressing gpNMB. In the ITT population, there were 78 patients in the glembatumumab vedotin arm and 43 patients in the capecitabine arm with ≥ 25 to 50% gpNMB overexpression and 140 patients in the glembatumumab vedotin arm and 65 patients in the capecitabine arm with > 50% gpNMB overexpression. In the response-evaluable population, there were 61 patients in the glembatumumab vedotin arm and 42 patients in the capecitabine arm with ≥ 25 to 50% gpNMB overexpression and 118 patients in the glembatumumab vedotin arm and 57 patients in the capecitabine arm with > 50% gpNMB overexpression. In this population of gpNMB-overexpressing patients, there was no improved benefit in PFS, OS, ORR, or DOR for glembatumumab vedotin relative to capecitabine in either gpNMB expression subgroup. gpNMB expression intensity did not clearly correlate with the outcomes of PFS, OS, ORR, or DOR in patients treated with glembatumumab vedotin.

Safety:

The overall median durations of glembatumumab vedotin and capecitabine treatment were 2.9 and 2.1 months, respectively.

All patients in the safety population (N = 305) reported at least one TEAE except for 2 patients in the glembatumumab vedotin treatment arm. The majority of patients, i.e., either glembatumumab vedotin (95.8%) or capecitabine (91.3%), reported treatment-related treatment-emergent AEs (TRAEs). Approximately 70% and 57% of patients experienced ≥ grade 3 TEAEs in the glembatumumab vedotin and capecitabine arms, respectively. Approximately 54% and 37% of patients experienced ≥ grade 3

TRAEs in the glembatumumab vedotin and capecitabine arms, respectively. Overall, a total of 90 (29.5%) patients experienced serious adverse events (SAEs): 71 (33%) patients in the glembatumumab vedotin arm and 19 (21%) patients in the capecitabine arm. Thirty-seven (17%) patients and 7 (8%) patients experienced serious TRAEs in the glembatumumab vedotin and capecitabine arms, respectively. In the glembatumumab vedotin arm, four (1.3%) patients had a fatal SAE (i.e., grade 5) of sepsis/septic shock/sepsis syndrome. One fatal event was assessed as treatment-related and three fatal SAEs were deemed not related to treatment by the investigators; however, Celldex assessed two of the four fatal cases as related to study treatment. Sepsis was discussed with the IDMC who recommended that the study protocol be amended to mitigate the risk of sepsis but that the study should continue as planned. The IDMC had no other safety recommendations during the conduct of the study. There were no deaths due to TEAEs or TRAEs in the capecitabine arm.

A total of 41 (13%) patients overall had a TEAE that resulted in study drug discontinuation: 31 (15%) patients in the glembatumumab vedotin arm and 10 (11%) patients in the capecitabine arm. At final analysis, a total of 199 (61%) deaths had occurred in the ITT population. The incidence of patient deaths were evenly distributed between treatment groups, and most patients died from disease progression.

The most common TEAEs (occurring in > 40% of patients) in the glembatumumab arm were fatigue, nausea, rash, and alopecia. The most common TEAEs (occurring in > 40% of patients) in the capecitabine arm were fatigue, nausea, diarrhea and palmar-plantar erythrodysesthesia. Overall, the safety profile of glembatumumab vedotin was as expected and similar to the experience in other clinical studies in advanced breast cancer and melanoma. However, there was no safety advantage over capecitabine.

CONCLUSIONS:

Glembatumumab vedotin demonstrated clinical activity but did not demonstrate an improvement in benefit/risk relative to capecitabine. The primary analysis did not show an improvement in PFS for glembatumumab vedotin vs. capecitabine. Additionally, there was no significant advantage for glembatumumab vedotin in the secondary endpoints of OS, ORR, and DOR, nor in any planned subgroups. gpNMB expression intensity in archived tumor epithelial cells as assessed by immunohistochemistry at a central lab did not clearly correlate with outcome in gpNMB expression subgroups. A post hoc, retrospective subgroup analysis suggested the greatest benefit from glembatumumab vedotin was in potentially taxane-sensitive disease. The safety profile of glembatumumab vedotin was consistent with the prior clinical experience.

Date of Report: 09 Nov 2018