2 SYNOPSIS

Name of Sponsor/Company: Celldex Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Drug: Rindopepimut (CDX-110)		
Name of Active Ingredient: Rindopepimut		

Study Title: An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The "ACT IV" Study; Protocol CDX110-04)

Investigators/Centers/Countries: Conducted at 165 study sites in 22 countries.

Studied Period: Date first subject dosed: 12 Apr 2012 Date last subject terminated: 15 Apr 2016[1]	**Phase of Development:** 3

Publications (reference):

M. Weller, N. Butowski, D. Tran, et. al. "ATIM-03. ACT IV: AN INTERNATIONAL, DOUBLE-BLIND, PHASE 3 TRIAL OF RINDOPEPIMUT IN NEWLY DIAGNOSED, EGFRvIII-EXPRESSING GLIOBLASTOMA" Neuro Oncol (2016) 18 (suppl_6): vi17-vi18.

Objectives:

The primary objective was:

- To confirm that the addition of rindopepimut to adjuvant temozolomide (TMZ) improves overall survival (OS) in patients with newly diagnosed, resected, EGFRvIII-positive glioblastoma with minimal residual disease (MRD).[2]

The secondary objectives were:

- Compare progression-free survival (PFS) between the two treatment arms.
- Further characterize the safety and tolerability profile of rindopepimut in combination with TMZ.

[1] Represents last patient visit prior to analysis cut-off date of April 29, 2016. Patients in the rindopepimut group who remained on treatment and were experiencing clinical benefit, in the opinion of the treating investigator, were subsequently allowed to continue rindopepimut through ACT IV until activation of an appropriate compassionate access protocol. The last patient transferred to a compassionate access protocol on December 1, 2016.

[2] Although the protocol and statistical analysis plan [SAP] refer to the mITT population as those patients with gross-total resection (GTR), the clinical study report and statistical output utilize the more accurate terminology of "minimal residual disease" [MRD] to describe this population. This revision represents an adjustment in terminology only – no definitions for identification of populations have been changed.

- Assess health-related quality of life (QOL) and symptom severity/interference using the patient-reported tools, European Organisation for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire (QLQ-C30) and Brain Cancer Module (BN20), and the M.D. Anderson Symptom Inventory - Brain Tumor (MDASI-BT).
- Compare objective tumor response rates between the two treatment arms (applicable only for patients with evaluable disease at study entry, as defined per Response Assessment in Neuro-Oncology [RANO] criteria).

The correlative objectives were:

- Further characterize the EGFRvIII-specific immune response to rindopepimut and the overall immunogenicity of the vaccine.
- Assess whether treatment with rindopepimut results in elimination of EGFRvIII expression.

Methodology: The ACT IV study was an international, randomized, double-blind, controlled study designed to demonstrate that rindopepimut improves overall survival (OS) when administered with standard temozolomide to patients with newly diagnosed, EGFRvIII positive glioblastoma and MRD. The extent of residual disease (whether MRD or SRD) was retrospectively determined by the central IRC. Patients with SRD formed a second exploratory cohort that had not been included in prior studies. The primary endpoint was powered and restricted to the MRD patient population.

Eligible patients were stratified by MGMT promoter methylation status, the European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class, and geographic region (North America and Western Europe vs. all other regions), and randomized to the treatment groups in a 1:1 ratio.

Brain MRIs were performed within 14 days after completion of chemoradiation, every 8 weeks for six months, every 12 weeks through the second year, every 16 weeks through the fourth year, and every 26 weeks thereafter, or until documented disease progression. Tumor response and progression were assessed per the Response Assessment in Neuro-Oncology (RANO) Working Group criteria, with minor modifications for the purpose of protocol standardization. Local investigator assessments guided individual treatment decisions. The retrospective IRC review, blinded to treatment assignment and investigator assessments, was utilized for the primary analyses of PFS and objective tumor response rate (ORR).

Safety assessments included monthly 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 M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) and EORTC Core Quality of Life Questionnaire (QLQ-C30) and Brain Cancer Module (BN20) were completed monthly throughout treatment by patients who were fluent in a language in which the questionnaires were validated.

Number of Subjects (Planned and Analyzed):

Planned: 374 MRD patients were planned for the mITT (primary analysis) population. Patients with incomplete resection (≥2 cm2 of residual tumor) were also eligible to participate in the study, bringing the anticipated total number of enrolled patients to approximately 700.

Analyzed: 745 patients were randomized to receive rindopepimut (n=371) or control (n=374) and were included in the ITT population. Of these, 405 patients (n=195 for the rindopepimut group and n=210 for the control group) were assigned to the mITT population (ie, the primary analysis population, consisting of patients with MRD) by central review, and 338 patients (n=175 for the rindopepimut group and n=163 for the control group) were assigned to the incomplete resection population.

Diagnosis and Main Criteria for Inclusion: The study was open to men and women ≥18 years of age with newly diagnosed EGFRvIII-expressing glioblastoma. Confirmation of glioblastoma histology and EGFRvIII expression analysis from resected tissue by real-time polymerase chain reaction (RT-PCR) were performed centrally (LabCorp, Research Triangle Park, NC, USA). Patients must have undergone maximal surgical resection and have completed standard radiation (up to 60 Gy) with concomitant temozolomide (75 mg/m2 per day). In order to be eligible, at least 90% of the planned radiotherapy dose had to be delivered. Disease progression during chemoradiation, any additional tumor-specific treatment for glioblastoma, inability to taper corticosteroid to ≤2 mg of dexamethasone (or equivalent) per day for at least 3 days prior to randomization, ECOG performance status ≥3 in the week prior to randomization, diffuse leptomeningeal disease, gliomatosis cerebri, infratentorial disease, metastatic disease, active infection, and immunosuppressive disease were exclusionary. All patients provided written informed consent. Full eligibility criteria can be found in the trial protocol.

An independent imaging review committee (IRC; BioClinica, Princeton, NJ, USA) evaluated post-operative and post-chemoradiation brain MRIs, and retrospectively classified patients as having either minimal residual disease (MRD; <2 cm2 of residual enhancing tumor on post-chemoradiation imaging) or incomplete resection (≥2 cm2 of residual enhancing tumor on post-chemoradiation imaging).

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

Rindopepimut (CDX-110): A vaccine consisting of a 14 amino-acid synthetic peptide (13 amino acids from EGFRvIII plus a cysteine residue; termed EGFRvIII peptide) covalently linked to the carrier protein Keyhole Limpet Hemocyanin (KLH); 0.8 mL containing approximately 500 mcg rindopepimut and 150 mcg GM-CSF administered via intradermal injections. Lots used include A1200126, B0011, B0013, P58605ARG.

GM-CSF: Leukine® (sargramostim); yeast-derived, recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF); administered via intradermal injections. Lots used include B15195, B17684, B19739, B19946, B20641, B21696A.

Blinded Control, Dose and Mode of Administration, Batch Number(s):

Keyhole Limpet Hemocyanin (KLH): VACMUNE® (Biosyn Corporation); a high purity, clinical grade, well-characterized aqueous formulation of a mixture of KLH 1 and KLH 2 immunocyanin subunits purified from native KLH, the high molecular mass hemocyanin of the giant keyhole limpet Megathura Crenulata, which has been reformulated and lyophilized by Celldex; 0.8 mL containing 100 mcg of KLH administered via intradermal injections. Lots used include 1-FIN-1145, 1-FIN-1646, 1-FIN-1947.

Adjuvant Treatment, Dose and Mode of Administration, Batch Number(s):

Temozolomide (TMZ): TEMODAR® (Merck); oral or intravenous administration according to the instructions in the product label and per standard practice; typical dose is 150 mg/m^2 body surface area per day for the first cycle and may increase to 200 mg/m^2 body surface area per day in subsequent cycles. Commercial supplies were used.

Treatment Regimen and Duration of Treatment:

All patients were to receive standard maintenance temozolomide at a dose of 150-200 mg/m^2 for five of 28 days, for 6-12 cycles, or longer if consistent with local standard of care. In addition, patients randomized to the rindopepimut group received 500 µg of rindopepimut admixed with 150 µg GM-CSF (Leukine®, Sanofi-Aventis), while the control group received 100 µg KLH (raw material from Biosyn, Carlsbad CA, USA; formulation/fill by Celldex). Each 0.8 mL dose was administered as 2-8 separate intradermal injections into the skin of the thigh below the groin. Experimental treatment was to start 7-

14 days after completion of standard chemoradiation, and was administered as two initial priming doses (study days 1 and 15), then monthly on day 21 of each temozolomide cycle and continuing after the end of maintenance temozolomide until disease progression or intolerance.

Criteria for Evaluation:

Efficacy:

- Overall survival (OS)
- Progression-free survival (PFS)
- Objective response rate (ORR)
- Health-related QOL

Pharmacodynamics:

- Post-treatment EGFRvIII expression status

Immunogenicity:

- Humoral immune responses to EGFRvIII
- Human leukocyte antigen (HLA) typing

Safety: Safety was assessed by the incidence and severity of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs), vital sign measurements, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, neurological examinations/MMSE, and WHO-ECOG performance status. Injection site reactions were measured by patients between 48 to 72 hours following each injection of double-blind vaccine, utilizing a template provided by Celldex.

Statistical Methods: The extent of residual disease (whether MRD or incomplete resection) was retrospectively determined by the central IRC. Patients classified with MRD by the IRC were included in the "modified" intent-to-treat (mITT) population for primary analysis. A total of 283 deaths in the MRD population at the time of the final analysis was calculated to provide 80% power to detect a target hazard ratio (HR) of 0.714, which corresponded to a 6-month improvement in median OS (from 15 months for control to 21 months for rindopepimut). The targeted number of deaths was based on 1-sided log-rank test, overall type I error rate of 0.025, and 2 planned interim analyses of OS for superiority using an O'Brien-Fleming group sequential monitoring plan. Allowing for a 48-month accrual period and 10% attrition rate, a sample size of 374 MRD patients was expected to result in 283 deaths within 72 months of the first randomized patient.

OS and PFS were calculated from the date of randomization and summarized using the Kaplan-Meier method. Primary inferential comparisons between treatment groups used the log-rank test stratified by MGMT promoter methylation status, adapted RPA class, and geographic region. HR were estimated using a stratified Cox proportional hazards model (SAS version 9.4). The stratification for the primary analysis of OS was based on the corrected stratification factors in the clinical database, given that about 20% of patients were randomized using a stratification factor not consistent with the actual clinical data.

Supportive secondary analyses were performed for all randomized patients (ITT) and for the patients who were classified with incomplete resection by the IRC. The sample size for incomplete resection patients was not prospectively defined. To control the family-wise error rate, study analyses were to proceed according to a fixed sequence procedure in which the primary analysis was completed for the MRD and ITT populations sequentially, followed by the secondary endpoint analyses.

ORR, time to response, and duration of response were summarized for all patients with measurable, enhancing tumor on post-chemoradiation MRI per IRC assessment (i.e., the "response evaluable" population).

Safety analyses included patients who received at least one dose of study treatment.

Supportive analysis of efficacy were also performed utilizing the "per-protocol" population, which excluded patients with important deviations from the protocol with the potential to substantially affect the results of the primary analysis.

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

Two interim analyses were planned and conducted for superiority and futility after 142 and 212 deaths, representing 50% and 75% of the events required for final analysis of the mITT population. Early stopping boundaries for superiority according to an O'Brien-Fleming alpha spending were p=0.002 and p=0.018 for the first and second interim analyses, respectively. HRs of ≥1.1 and >0.9 represented boundaries for futility.

SUMMARY OF RESULTS

At the second preplanned interim analysis (data cutoff: 24 Oct 2015) with 212 OS events, the futility boundary was crossed. The OS HR for rindopepimut vs. control in the mITT population was 0.99 (95% CI: 0.74, 1.31), suggesting that rindopepimut was unlikely to be found superior to control. The study was therefore closed. Additional survival information was obtained as patients were discontinued from the study, and final analyses were conducted with a data cutoff of 29 Apr 2016.

Study Population: Between 12 Apr 2012 and 15 Dec 2014, 745 patients were randomized to receive rindopepimut (n=374) or control (n=371) and were included in the ITT population. Of these, 405 patients (n=195 for the rindopepimut group and n=210 for the control group) were assigned to the mITT population (ie, the primary analysis population) by central review, and 338 patients (n=175 for the rindopepimut group and n=163 for the control group) were assigned to the incomplete resection population. Four patients were randomized but did not receive treatment; these included two patients with incomplete resection in the rindopepimut group and two patients (one MRD, one incomplete resection) in the control group. At study closure and final analysis, 523 deaths in the ITT population, 264 deaths in the mITT population, and 258 deaths in the incomplete resection population had occurred.

Pretreatment demographic, baseline, and disease characteristics were well balanced between treatment groups within each analysis population.

Efficacy: Overall survival did not differ significantly between the treatment groups for the mITT population (HR 1.01, 95% confidence interval [CI] 0.79 – 1.30; p=0.9226), ITT population (HR 0.89, 95% CI 0.75 – 1.07; p=0.2224), or the incomplete resection population (HR 0.79, 95% CI 0.61 – 1.02; p=0.0660). Median OS (months) for the rindopepimut and control groups, respectively, was 20.1 (95% CI 18.5 – 22.1) vs. 20.0 (95% CI 18.1 - 21.9) in the mITT population, 17.4 (95% CI 16.1 – 19.4) vs. 17.4 (95% CI 16.2 – 18.8) in the ITT population, and 14.8 (95% CI 12.8 – 17.1) vs. 14.1 (95% CI 12.6 – 15.7) in the incomplete resection population.

However, a trend for long-term survival benefit was observed in the incomplete resection population, with a 2-year survival rate of 29.7% (95% CI 22.6 – 37.1) in the rindopepimut group vs. 18.7% (95% CI 12.5 – 25.7) in the control group (p=0.0293). Pre-planned and ad-hoc subgroup analyses demonstrated that this apparent treatment effect in the incomplete resection population was most pronounced for patients treated in the United States (HR 0.70, 95% CI 0.51-0.96; p=0.027), who developed anti-

EGFRvIII humoral response at a "moderate" rate (HR 0.57, 95% CI 0.39-0.83; p=0.003), and who received nitrosoureas in the post-treatment follow-up period (HR 0.49, 95% CI 0.25-0.97; p=0.038). No biologically plausible explanations for these findings were identified, and subgroup analyses of the MRD population did not demonstrate similar findings. A weaker trend for improved long-term survival was seen in the group of patients who were classified in the incomplete resection population according to investigator assessments (HR 0.91, 95% CI 0.71 – 1.18; p=0.4772), with a 2-year survival rate of 29.9% (95% CI 22.9 – 37.3) in the rindopepimut group vs. 19.9% (95% CI 13.7 – 26.9) in the control group (p=0.0464).

Anticancer therapies received in the post-treatment follow-up period were well balanced among treatment groups. Although there were geographic differences in the type of anticancer therapies used after progression, with more frequent use of nitrosoureas in the European Union and more frequent use of bevacizumab in the United States, these regional differences did not appear to account for the geographic variability observed within the overall survival analyses.

Progression-free survival was similar for the treatment groups within the mITT population (HR 1.01, 95% CI 0.80 – 1.29; p=0.9106), ITT population (HR 0.94, 95% CI 0.79 - 1.13; p=0.5149), and the incomplete resection population (HR 0.86, 95% CI 0.66 – 1.12; p=0.2787).

The ORR in the response-evaluable population for both treatment groups was approximately 15% (95% CI approximately 10 – 21).

No statistically significant differences in quality of life measures or requirement for corticosteroids were observed among the analysis populations.

Safety: The overall median durations of study vaccine (rindopepimut or KLH) and adjuvant TMZ in all patients were 6.6 and 4.8 months, respectively.

Nearly all (96.5%) of the patients in the Safety population reported at least one TEAE. The majority of patients reported TEAEs that were considered related to study vaccine (overall 72.1%) or TMZ (overall 70.2%). Most of the subjects overall (approximately 53%) reported TEAEs that were grade 1 or 2 severity; most of the related TEAEs reported (to either study vaccine or TMZ) were grade 1 or 2 severity. A total of 198 patients (26.7%) overall experienced treatment-emergent SAEs; and 14 patients (1.9%) overall experienced a fatal SAE (ie, grade 5). A total of 48 patients (6.5%) overall had a TEAE that resulted in study drug discontinuation. At study closure and final analysis, overall 523 and 264 deaths had occurred in the ITT and mITT populations, respectively. Patient deaths were evenly distributed between treatment groups, and most patients died from disease progression.

The greatest difference in TEAEs between the study groups was in injection site AEs, which were the most common TEAEs reported for the rindopepimut group and were also nearly twice as prevalent in the rindopepimut group compared to the control group. Injection site reactions, consisting chiefly of transient grade 1-2 erythema, pruritus, and rash, were experienced by the majority of the patients who received rindopepimut, but were also common in the control group.

EGFRvIII Expression: In the small subset of patients with available post-treatment tumor sample, EGFRvIII expression was eliminated for 16 of 28 (57%) rindopepimut-treated patients and 17 of 26 (65%) patients in the control group. Mean anti-EGFRvIII titer was not significantly different between the groups of patients with either elimination or persistence of tumor EGFRvIII. Elimination of EGRFvIII did not consistently or significantly correlate with efficacy outcomes.

Immunogenicity: Rindopepimut treatment resulted in a robust humoral response, with treated patients reaching a median peak anti-EGFRvIII antibody titer of 1:25,600 in the Safety population. The magnitude of response was similar between the mITT (ie, minimal residual disease) and incomplete resection populations, and consistent with that seen in prior studies of rindopepimut. The use of

corticosteroids did not appear to have a significant impact on the rindopepimut-induced humoral immune response. However, no clear correlation between rapid or robust titer response and clinical outcome was observed.

CONCLUSIONS: The ACT IV Study was the most comprehensive study of patients with EGFRvIII-expressing glioblastoma conducted to date. Despite the strong anti-EGFRvIII immune response generated in patients, the primary study analysis did not demonstrate a survival benefit for patients with MRD who received rindopepimut with TMZ. The outcome for patients treated with rindopepimut was similar to that observed in prior studies. Median OS for MRD patients treated with rindopepimut in this study was 20.1 months, which is consistent with the range of 20-22 months observed in prior trials in the same population. Of note, the definition for MRD was increased to <2 cm^2 in the ACT IV study, as compared to ≤ 1 cm^2 in prior studies. However, patients in the control arm experienced median survival of 20.0 months from randomization, which is markedly better than the matched control datasets available at the time of study design suggesting an expected median survival of 12-16 months from randomization.

A trend for long-term survival benefit was observed in a subset of patients with significant residual disease. No imbalances were found that might have accounted for this potential signal of differential activity. Baseline prognostic characteristics, corticosteroid dosing, and subsequent therapies were well balanced between both treatment groups. However, this apparent treatment effect in the incomplete resection population was not consistent across geographic regions, the effect was less pronounced when tumor burden was defined by the investigator as opposed to central review, and the magnitude of humoral immune response did not consistently correlate with presumed treatment benefit or extent of residual disease.

Rindopepimut was very well tolerated. Injection site reactions, consisting chiefly of transient grade 1-2 erythema, pruritus, and rash, were experienced by the majority (80%) of patients who received rindopepimut, but were also common (41%) in the control group. Despite the observation of hypersensitivity reaction attributed to rindopepimut in prior studies, such events were infrequent in both treatment groups. There was similarly no evidence for increased toxicity that might theoretically arise due to rindopepimut-induced immune infiltration of the brain, such as cerebral edema or seizure.

In conclusion, primary study analysis did not demonstrate a survival benefit for patients with MRD who received rindopepimut with TMZ. Nonetheless, the trend towards improved long-term survival in the incomplete resection population may challenge the view that minimal tumor burden is required for immunotherapy to be effective. Rindopepimut was associated with a survival advantage (HR 0.53, 95% CI 0.32-0.88; p=0.01) when combined with bevacizumab in a small phase 2 trial of patients with recurrent disease (ReACT), where per study design patients were not required to have MRD. These data might suggest that a certain level of antigen exposure is necessary for an efficacious immune response. It is also possible that combination with temozolomide may compromise an immunological effect, in contrast with bevacizumab. Taken together with the ReACT study results, the ACT IV data may lend support to the design of innovative clinical trials targeting multiple tumor antigens or combining angiogenesis inhibition with immunotherapy.

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