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Celldex Therapeutics' Rindopepimut Demonstrates Promising Clinical Activity in Patients with EGFRvIII-positive Recurrent Glioblastoma at SNO

Strong interim survival trend (12.0 vs 7.9 months) emerging in ongoing bevacizumab naive randomized cohort; 5.6 month median OS (48% > 6 months) in bevacizumab refractory single-arm cohort; robust anti-tumor immune responses were generated among heavily pre-treated patients with recurrent tumors and these responses correlate with improved outcome

Rindopepimut demonstrates ability to significantly shrink recurrent and refractory glioblastomas

Long-term survival update also provided for three Phase 2 frontline studies; EGFRvIII patients continue to exceed expectations with 14% 5-year survival vs 0% historical control

HAMPTON, N.J., Nov. 24, 2013 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. (Nasdaq:CLDX) today reported interim data from its ongoing, exploratory Phase 2 ReACT study of rindopepimut in recurrent glioblastoma. Rindopepimut is an immunotherapeutic vaccine that targets the tumor specific oncogene EGFRvIII(v3). Patients with EGFRvIII-positive glioblastoma typically have a worse prognosis than the overall glioblastoma population, including poor long term survival. The ReACT results demonstrate promising signs of clinical activity in advanced patient populations, including patients both naïve and refractory to bevacizumab (Avastin®). An update on long-term survival for the three completed Phase 2 frontline studies in EGFRvIII-positive glioblastoma was also presented and results continue to exceed outcomes seen in contemporary controls. A webcast/conference call will be held at 8:30 am ET on Monday, November 25th, to discuss the results (details provided below).

The data were presented in an oral session by David A. Reardon, M.D., Clinical Director, Center for Neuro-Oncology, Dana-Farber Cancer Center and Associate Professor of Medicine, Harvard Medical School and the lead investigator of the ReACT study, at the 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in conjunction with the 18th Annual Meeting of the Society for Neuro-Oncology (SNO).

"Patients who have grown right though Avastin are resistant to all of our available therapies," said David Reardon, M.D. "The potent immune response generated by rindopepimut and preliminary signs of anti-tumor activity in the Avastin refractory patients in the ReACT study are very exciting. The additional signal of an improved survival outcome in Avastin naïve patients further supports the potential activity of rindopepimut. I look forward to the final results of this study and hope they confirm what we have seen so far."

"Expectations for a vaccine to be active in this patient population were very low," said Thomas Davis, M.D., Senior Vice President and Chief Medical Officer of Celldex. "If these multiple signals for immunologic and anti-tumor activity persist in the final data, it may establish a new perspective on the potential for immunotherapy. These early results have led to the expansion cohort and we are beginning to plan additional studies of combinations that could further improve efficacy."

ReACT is a Phase 2 exploratory study designed to determine if adding rindopepimut to standard of care bevacizumab improves the outcomes for patients with EGFRvIII-positive recurrent glioblastoma across multiple measures. As originally designed, the study included 2 groups:

- Group 1 - bevacizumab naive, n= apx. 70, enrollment ongoing—patients randomized to receive either rindopepimut or KLH (administered as a control), each along with bevacizumab
- Group 2 - bevacizumab refractory, n= apx. 25, enrollment completed—patients receive rindopepimut plus bevacizumab in a single treatment arm

In August 2013, Celldex announced that enrollment had been completed in Group 2 and that, based on early evidence of anti-tumor activity, an expansion cohort of approximately 75 patients (Group 2C) would be added to better characterize the potential activity of rindopepimut in this refractory patient population. As amended, the ReACT study will enroll approximately 170 patients.

Clinical Activity Overview

Group 1- Recurrent GBM; bevacizumab naive

Interim results are available for the first 40 patients enrolled [rindopepimut + bevacizumab (n=20); control + bevacizumab n=20)]. 12 patients continue to receive treatment and 27 continue to be followed for survival. While the data continue to mature, trends toward both an overall survival (OS) and progression-free survival (PFS) benefit have been observed on the rindopepimut arm to date.

Interim ReACT Overall Survival and Progression-free Survival Bevacizumab-Naïve Recurrent GBM

	Rindo + Bev (n=20)	Control + Bev (n=20)	
OS	12.0 months	7.9 months	HR = .43 (0.13, 1.44) ; p=0.16
PFS	3.7 months	2.0 months	HR= .74 (0.34, 1.61); p=0.47

The study suggests that early development of high anti-EGFRvIII titer may be predictive of improved outcomes in this patient population, as improved survival was associated with rapid generation of a robust humoral response. All 8 patients on the rindopepimut arm that developed high titers by day 57 are still alive to date (range of 3.6+ to 17.0+ months). For the remaining 10 patients who did not develop high titers by day 57, 5 remain alive (range of 3.8+ to 12.9+ months). Consistent with the premise that EGFRvIII-positive patients fare worse than the general glioblastoma population, results to date suggest that the EGFRvIII-positive patient population had a lower OS in the Control + Bevacizumab arm than was observed in the bevacizumab registration study (AVF3708g) in recurrent glioblastoma in all-comers (7.9 months OS, ReACT vs 9.3 months OS AVF3708g).

14 out of 18 (78%) patients with measurable disease on the rindopepimut arm experienced any tumor shrinkage versus 9 out of 16 (56%) patients on the control arm. Assessments of response were conducted by study investigators according to RANO criteria. Cases with greater than a 25% reduction in area of measurable disease were also reviewed by an expert panel blinded to treatment assignment.

Preliminary Analysis of Objective Response Bevacizumab-Naïve Recurrent GBM

	Rindo + Bev	Control + Bev
ORR (confirmed CR/PR)[1,2]	3/19 (16%)**	2/16 (13%)**
Any response (> 50% shrinkage) including those not sustained at subsequent assessment[1]		
By Investigator review	7/19 (37%)	3/16 (19%)
By Expert Panel review	6/19 (32%)	4/16 (25%)
By Either review	9/19 (47%)	4/16 (25%)

**Two additional patients in the rindopepimut arm and 1 in the control arm have experienced greater than 50% shrinkage by either investigator or expert panel review and are pending follow up for confirmation of response. [1]Response-evaluable patient subset with measurable disease. [2]All concordant between investigator and expert panel review

70% of patients in the rindopepimut arm had stable disease or better for greater than 2 months versus 55% in the control arm. Further emphasizing the benefit in disease control, only 5% of patients treated with rindopepimut required an increase in steroids versus 35% of patients on the control arm.

Group 2- Recurrent GBM; bevacizumab refractory [defined as having progressed (grown through) by RANO criteria within two months of prior bevacizumab treatment]

Results are available for all 25 patients enrolled in this arm. One patient continues to receive treatment and 6 continue to be followed for survival.

ReACT Overall Survival and Progression-free Survival Bevacizumab-Refractory Recurrent GBM

	Median, months 95% CI
OS	5.6 (3.2, 6.7)
PFS	1.9 months (1.8, 2.8)

PFS results in this refractory population may be more consistent with the profile of an immunotherapy candidate where PFS

does not always correlate directly with an overall survival benefit. The median OS of 5.6 months is noteworthy in these heavily pretreated, refractory EGFRvIII-positive patients. A review of the literature assessing survival in recurrent patients who are bevacizumab experienced across eight independent studies suggests a weighted-average survival of 3.6 months (range of 2.6 to 5.8 months) in all-comers. It is important to note that these eight studies do not necessarily meet the strict definition of refractory applied in the ReACT study and that these studies included EGFRvIII-negative patients who tend to perform better.

Again, results suggest that early development of high anti-EGFRvIII titer may be predictive for improved outcome in this patient population as improved survival was associated with rapid generation of a robust humoral response. For the 13 patients with high titers by day 57, median OS was 6.6 months versus 3.2 months for the 11 patients who did not develop high titers (HR = .33 (0.08, 0.67); p=0.009). 69% of patients with high titers were alive at 6 months compared to 18% of patients who did not develop high titers. With no comparative data available to define expected outcome for EGFRvIII-positive patients who have failed bevacizumab, an ambitious goal of progression-free survival of 20% at 6 months was established as the primary endpoint for this arm; 2 out of 25 (8%) patients are progression-free at six months.

Six out of 24 patients with measurable disease experienced any tumor shrinkage. Assessments of response were conducted by study investigators according to RANO criteria. Cases with greater than a 25% reduction in area of measurable disease were also reviewed by an expert panel blinded to treatment assignment. Per the investigator review, 4 patients experienced significant tumor shrinkage; however, two of these were deemed protocol violations because while the patient had prior bevacizumab exposure, they did not meet the strict definition of bevacizumab refractory as outlined in the ReACT protocol. 32% of patients had stable disease or better for greater than 2 months.

Preliminary Analysis of Objective Response Bevacizumab-Refractory Recurrent GBM

Patient	Investigator Assessment	Expert Panel Review
1	PR (79% shrinkage)	SD*
2	90% shrinkage; not sustained	SD*
Patients with progression > 2 months after discontinuation of bevacizumab:		
3	CR (9.3 months duration)	SD*
4	100% shrinkage; not sustained	PR

*Enhancement judged not measureable, but thought to improve on treatment

Immune Response Overview

Remarkably robust humoral responses comparable or exceeding those seen in the frontline setting (ACT III) were observed despite advanced disease, use of steroids, prior chemotherapy exposure and the presence of bulky tumor. There was a four-fold increase in anti-EGFRvIII antibody titers in 84% of bevacizumab-naïve patients and 79% of bevacizumab-refractory patients. A high-titer response was noted (range of 1:12,800 to 1:6,553,600) in 50% of bevacizumab-naïve patients and 67% of bevacizumab-refractory patients and titers increased with time on study. Importantly, the study suggests that early development of anti-EGFRvIII titer may be predictive of improved outcomes in this patient population as improved survival was associated with rapid generation of humoral response. These results also provide further support for the rindopepimut/bevacizumab combination approach, as prior studies have suggested that bevacizumab can enhance immune-mediated anti-tumor effects in tumor model and may, in turn, optimize EGFRvIII specific immune response.

Safety

Across both Group 1 and Group 2, rindopepimut plus bevacizumab was very well tolerated (dosing up to 13+ months). There were no unexpected toxicities associated with concomitant bevacizumab administration and there were no treatment-related toxicities resulting in discontinuation of study treatment. Adverse events were consistent with prior studies of rindopepimut.

Phase 2 Frontline Long-term Overall Survival Assessments (ACT III, ACT II and ACTIVATE)

Celldex also announced today the presentation of four- and five-year survival data from the Phase 2 rindopepimut clinical program (3 studies; pooled n=105) in EGFRvIII-positive glioblastoma. Across three Phase 2 studies of rindopepimut, survival data remains consistent and suggests a substantial and continuing survival benefit in comparison to independent control datasets (see chart below) at the median and at all other time points evaluated.

Phase 2 Frontline Long-term Overall Survival Assessments (ACT III, ACT II and ACTIVATE)

	Median, Years	2-year	3-year	4-year	5-year

	(95% CI)	rate	rate	rate	rate
Phase 2 Rindopepimut Studies, Pooled (n=105)	2.1 (1.8, 2.4)	51%	30%	18%	14%
Matched historical control (n=17)*	1.3 (0.9, 1.7)	6%	6%	0%	0%

*Patients treated at M.D. Anderson contemporaneously to ACTIVATE, matched for major eligibility requirements, including EGFRvIII+ GBM, GTR and no PD through CRT.

The pooled overall long-term survival results continue to be consistent with the ACT III Phase 2 study (18% for 4-years and 14% for 5-years). The Phase 3 registration study, ACT IV, is modeled after the ACT III study.

Webcast/Conference Call Information

Celldex management will host a conference call/webcast at 8:30 am ET tomorrow, Monday, November 25, 2013 to discuss the ReACT study results and the rindopepimut program. John F. de Groot, M.D., Associate Professor of the Department of Neuro-Oncology, Director of the Neuro-Oncology Fellowship Program and Director of Clinical Research in the Department of Neuro-Oncology, at the University of Texas MD Anderson Cancer Center in Houston, TX will join the call. Dr. de Groot served on the expert review committee for the ReACT study.

The conference call and presentation will be webcast live over the Internet and can be accessed by logging on to the Events & Presentations section under "Investors and Media" of the Celldex Therapeutics website at www.celldex.com. The call can also be accessed by dialing (866) 743-9666 (within the United States) or (760) 298-5103 (outside the United States). The passcode is 10297215.

A replay of the call will be available for approximately one week after the live call concludes through December 2, 2013. To access the replay, dial 855-859-2056 (within the United States) or 404-537-3406 (outside the United States). The passcode is 10297215.

About Rindopepimut

Rindopepimut is an investigational immunotherapy that targets the tumor specific oncogene EGFRvIII (v3), a functional and permanently activated variant of the epidermal growth factor receptor (EGFR), a protein that has been well validated as a target for cancer therapy. Expression of EGFRvIII correlates with increased tumorigenicity in mouse models and poor long term survival in clinical studies of patients with glioblastoma (GBM). In addition, EGFRvIII-positive cells are believed to stimulate proliferation of non-EGFRvIII cells through IL-6 cell-to-cell signaling and to release microvesicles containing EGFRvIII, which can merge with neighboring cells, transferring tumor-promoting activity. EGFRvIII expression may also be associated with tumor stem cells that have been identified in GBM. These stem cells contribute to resistance to cytotoxic therapy and tumor recurrence. EGFRvIII is expressed in tumors in about 30% of patients with GBM. It has not been detected at a significant level in normal tissues; therefore, targeting of this tumor-specific molecule is not likely to impact healthy tissues.

Three Phase 2 trials of rindopepimut—ACTIVATE, ACT II, and ACT III—have been completed in newly diagnosed EGFRvIII-positive GBM and have shown consistent improvements in both overall survival and median progression-free survival. The most common adverse events for rindopepimut include injection site reactions, fatigue, rash, nausea and pruritus. Rindopepimut is currently being studied in two clinical trials in EGFRvIII-positive GBM—an international Phase 3 study called ACT IV in newly diagnosed GBM and a Phase 2 study called ReACT in recurrent GBM.

About Celldex Therapeutics, Inc.

Celldex is developing targeted therapeutics to address devastating diseases for which available treatments are inadequate. Our pipeline is built from a proprietary portfolio of antibodies and immunomodulators used alone and in strategic combinations to create novel, disease-specific therapies that induce, enhance or suppress the body's immune response. Visit www.celldex.com.

Avastin is a registered trademark of Genentech, a member of the Roche Group.

Safe Harbor Statement Under the Private Securities Litigation Reform Act of 1995: *This release contains "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including those related to the Company's strategic focus and the future development and commercialization (by Celldex and others) of rindopepimut (CDX-110), Glembatumumab vedotin ("glemba"; CDX-011), CDX-1135, CDX-1401, CDX-1127, CDX-301, Belinostat and other products. Forward-looking statements reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events. Although management believes that the expectations reflected in such statements are reasonable, they give no assurance that such expectations will prove to be*

correct and you should be aware that actual results could differ materially from those contained in the forward-looking statements. Forward-looking statements are subject to a number of risks and uncertainties, including, but not limited to, our ability to successfully complete research and further development and commercialization of rindopepimut, glemba and other drug candidates, our ability to obtain additional capital to meet our long-term liquidity needs on acceptable terms, or at all, including the additional capital which will be necessary to complete the clinical trials that we have initiated or plan to initiate; our ability to adapt our APC Targeting Technology™ to develop new, safe and effective vaccines against oncology and infectious disease indications; our ability to successfully complete product research and further development of our programs; the uncertainties inherent in clinical testing; our limited experience in bringing programs through Phase 3 clinical trials; our ability to manage research and development efforts for multiple products at varying stages of development; the timing, cost and uncertainty of obtaining regulatory approvals; the failure of the market for the Company's programs to continue to develop; our ability to protect the Company's intellectual property; the loss of any executive officers or key personnel or consultants; competition; changes in the regulatory landscape or the imposition of regulations that affect the Company's products; and other factors listed under "Risk Factors" in our annual report on Form 10-K.

All forward-looking statements are expressly qualified in their entirety by this cautionary notice. You are cautioned not to place undue reliance on any forward-looking statements, which speak only as of the date of this release. We have no obligation, and expressly disclaim any obligation, to update, revise or correct any of the forward-looking statements, whether as a result of new information, future events or otherwise.

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