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# Celldex Presents Varlilumab Proof of Concept Data at SITC Annual Meeting 2014

## Favorable safety profile, clear biological effects and clinical activity position varlilumab for future studies

HAMPTON, N.J., Nov. 7, 2014 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. (Nasdaq:CLDX) today presented a comprehensive review of the Company's Phase 1 single-agent study of varlilumab, focusing on biomarker analyses and confirming significant immunological effects consistent with CD27 costimulation. Varlilumab is an immunotherapy designed to harness the body's natural immune response by enhancing the activation of T cells that can specifically recognize and kill cancer cells. The clinical and immunological activity data presented today add to a growing body of literature supporting the broad study of varlilumab in combination with a number of other anti-cancer agents including but not limited to checkpoint inhibitors, chemotherapies, targeted therapies and vaccines. Varlilumab will enter multiple combination studies in the coming months. The data were presented today in a poster session entitled, "Immune Correlates of Varlilumab (CDX-1127) Treated Cancer Patients are Consistent with CD27 Costimulatory Activity" at the Society for the Immunotherapy of Cancer (SITC) Annual Meeting.

"In this first-in-man study of varlilumab, we have observed a consistent pattern of immunologic changes that correspond with the immune activating effect of the antibody," said Tim Bullock, PhD, Associate Professor of Pathology, University of Virginia School of Medicine, who led the immune monitoring of the Phase 1 varlilumab study. "Some of the salient features include the release of serum cytokines, activation of T cells, an expansion of Natural Killer cells and a decrease in regulatory T cells. Interestingly, these immunologic changes were most prominent in the dose escalation patients that had a delay between their first dose and subsequent doses, suggesting that less frequent dosing of varlilumab may provide optimal immunologic effects."

"We believe the Phase 1 experience with varlilumab has established clear proof of concept for this program by demonstrating a benign safety profile, clear biological effects that are consistent with the predicted mechanism of action, and enduring clinical responses in this advanced patient population," said Thomas Davis, MD, Executive Vice President and Chief Medical Officer of Celldex Therapeutics. "Based on these data, as well as the strong preclinical data supporting combination therapy, we are eager to see varlilumab through its next stage of clinical studies in combination with other therapies. Importantly, these studies are designed to investigate varying dosing regimens of varlilumab to identify the optimal dose and regimen when used in combination with other therapies."

**Immune Monitoring Assessments:**

The analyses included patients with solid tumors and hematologic malignancies from the dose escalation portion of the Phase 1 study (dosed at 0.1, 0.3, 1, 3 and 10 mg/kg with a one month delay between the initial dose and the four weekly multidoses) and patients from expansion cohorts in metastatic melanoma and renal cell carcinoma (dosed at 3 mg/kg weekly). All cohorts showed a consistent change in specific immune biomarkers, however the immune correlates were generally stronger or more consistent with the dose escalation portion of the study, suggesting that less frequent dosing may provide the best regimen for promoting sustained CD27 activation with varlilumab.

Pharmacokinetic (PK) assessments showed good exposure, including at lower dose levels, with a half-life of 10-13 days. Notably, no anti-varlilumab antibody responses have been detected to date and varlilumab demonstrated continuous binding to circulating T cells even at doses as low as 0.3 mg/kg for at least 29 days post infusion.

Biomarker analysis demonstrated significant immunological effects consistent with CD27 costimulation across all dose levels. A serum biomarker profile of the 1mg/kg cohort (selected because it had the largest patient population; n=9) demonstrated robust and transient stimulation of multiple cytokines and chemokines consistent with varlilumab activation of CD27 signaling. Further assessment of immune cell subsets demonstrated no depletion of B cells or CD8+ T cells, with a concomitant decrease in CD4+ T cells and regulatory T cells (Treg, CD4+ and FoxP3+). Evidence for functional activation of T cells was demonstrated by upregulation of the activation marker, HLA-DR and new or enhanced melanoma antigen-specific T cell responses in select melanoma patients.

**Safety and Clinical Overview:**

A total of 86 patients have been dosed. 55 patients have been dosed in dose escalation cohorts (various solid and hematologic B-cell tumors) and 31 patients have been dosed in the expansion cohorts (melanoma and RCC) at 3 mg/kg. In both the solid tumor and hematologic dose-escalations, the pre-specified maximum dose level (10 mg/kg) was reached without identification of a maximum tolerated dose. The majority of adverse events (AE) related to treatment have been mild to moderate (Grade 1/2) in severity, with only three serious AEs related to treatment reported. No significant immune-mediated adverse events (colitis, hepatitis, etc.) typically associated with check-point blockade have been observed.

Two patients experienced objective responses.

- A patient with Hodgkin lymphoma experienced a complete response after 3 cycles at 0.3 mg/kg, which continues at 18.9+ months. This patient's response was delayed and there was no detectable CD27 on their tumor cells leading the Company to conclude the response was immune-mediated response and not ADCC-mediated.

- A patient with renal cell carcinoma treated in the expansion cohort experienced a partial response after 1 cycle at 3 mg/kg that further improved on the second cycle and continues at 5.5+ months. This patient had five target lesions that have all regressed, including a lung lesion that has completely disappeared.

Thirteen patients experienced stable disease (SD) (3-25.5+ months), including:

- A patient with uveal melanoma (M1c) with SD for 11.5 months
- A patient with renal cell carcinoma with SD for 25.5+ months; and
- A patient with follicular lymphoma with SD for 14 months.

Based on the results observed in hematologic malignancies, an expansion cohort has been added to enroll up to 15 patients with Hodgkin Lymphoma and an abbreviated dose escalation in T cell hematologic malignancies is ongoing.

**About Varlilumab**

Varlilumab is a fully human monoclonal antibody that targets CD27, a critical molecule in the activation pathway of lymphocytes. CD27 can be effectively manipulated with activating antibodies to induce potent anti-tumor responses and may result in less toxicities due to its restricted expression and regulation. Varlilumab is a potent anti-CD27 agonist that induces activation and proliferation of human T-cells when combined with T-cell receptor stimulation. In lymphoid malignancies that express CD27 at high levels, CDX-1127 has an additional mechanism through a direct anti-tumor effect.

**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.

**Forward-Looking Statement**

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 ("rindo"; CDX-110), glembatumumab vedotin ("glemba"; CDX-011), varlilumab ("varli"; CDX-1127), CDX-1401, CDX-301 and other products and our goals for 2014. 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, glembatumumab vedotin 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; the uncertainties inherent in clinical testing and accruing patients for clinical trials; our limited experience in bringing programs through Phase 3 clinical trials; our ability to manage and successfully complete multiple clinical trials and the research and development efforts for our multiple products at varying stages of development; the availability, cost, delivery and quality of clinical and commercial grade materials produced by our own manufacturing facility or supplied by contract manufacturers, who may be our sole source of supply; 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 and quarterly reports on Form 10-Q.

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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