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Celldex Therapeutics' Varlilumab Continues to Demonstrate Very Favorable Profile

--Very well tolerated with notable immunologic and anti-tumor activity in Phase 1 Study; Will enter multiple combination studies in 2H 2014--
--Data presented at ASCO Annual Meeting 2014--

HAMPTON, N.J., June 2, 2014 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. (Nasdaq:CLDX) today reported data from its ongoing Phase 1 study of the fully human monoclonal antibody varlilumab (CDX-1127) in cancer. Varlilumab is an immunotherapy designed to enhance the body's natural immune response by directly activating T cells that can specifically recognize and kill cancer cells. Preclinical data support 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 at least four combination studies in the second half of 2014.

Results presented included data from the lymphoid malignancies dose-escalation arm and solid tumor expansion cohorts in metastatic melanoma and renal cell carcinoma. Varlilumab was very well tolerated and demonstrated clear biologic activity and promising signs of clinical activity in advanced, treatment-refractory patient populations—all of which provide the rationale for combination studies with other immune activating therapies. Results were presented in two poster sessions (poster #16 and 19) at the American Society of Clinical Oncology (ASCO) Annual Meeting 2014 on Monday, June 2, 2014 from 1:15 to 4:15 p.m. CDT. In addition, the data will be discussed during a Poster Highlight Session entitled "Modulating the Anti-tumor Immune Response" by Dr. Cassian Yee of The University of Texas MD Anderson Cancer Center today at 5:15 CDT.

"This first-in-man study for a CD27 agonist antibody documented significant immunological effects of varlilumab, most notably activation of T cells, including de novo responses to previously defined tumor antigens, and impressive decreases in regulatory cells—both of which have been shown to be necessary to generate optimal anti-cancer immune responses," said Tim Bullock, PhD, Associate Professor of Pathology, University of Virginia School of Medicine, who led the immune monitoring on the solid tumor arm of the Phase 1 varlilumab study. "Importantly, varlilumab was able to elicit these biological effects while also demonstrating a benign safety profile--suggesting that combination therapies involving varlilumab will not be limited by unacceptable toxicities. Moving forward, in these combination studies, it will be important to further elucidate how the dose and timing of varlilumab administration impact the biological and clinical effects so we can optimize clinical benefit for patients with cancer."

"Varlilumab's minimal toxicity and ability to specifically activate the immune system while acutely reducing measurable regulatory T cells make it an ideal agent to use with checkpoint inhibition and other anti-tumor approaches," said Tom Davis, MD, Senior Vice President and Chief Medical Officer of Celldex Therapeutics. "We are focused on the initiation of an expanded combination program with internal programs and external collaborators, including several checkpoint inhibitors and other molecularly targeted agents. We believe varlilumab has significant potential and these studies will further add to our understanding of this program."

Varlilumab 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 fewer 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, varlilumab may have an additional mechanism of action through a direct anti-tumor effect.

Study Overview:

This Phase 1 study of varlilumab includes two arms—lymphoid malignancies and solid tumors. Initial dose escalation cohorts (0.1, 0.3, 1, 3, or 10 mg/kg) were conducted in both arms to determine an optimal dose and no maximum tolerated dose was reached. The lymphoid malignancies dose escalation arm recently completed enrollment (n=24) and a new cohort has been added to include evaluation of T cell malignancies. The solid tumor arm, which included patients with various solid tumors, completed dose escalation last year and results were presented at the Society for the Immunotherapy of Cancer Annual Meeting. Two expansion cohorts were subsequently added at 3 mg/kg dosed weekly in metastatic melanoma (n=16) and renal cell carcinoma (n=15) to better characterize clinical activity and further define the safety profile in preparation for

combination studies. Patients on study had advanced disease and had received (or refused) all available approved therapy options. The median number of prior therapies is four anti-cancer (three cytotoxic) for lymphoid malignancies, one anti-cancer for metastatic melanoma and three anti-cancer for renal cell carcinoma. 13 of the 16 patients in the metastatic melanoma arm had checkpoint blockade prior to entering the varlilumab study; the remaining three refused or were determined by their physician to be ineligible for checkpoint blockade.

Safety, Pharmacokinetics and Immune Monitoring Overview:

As previously reported, varlilumab was very well tolerated with no indication of immune-mediated adverse events often seen with other immunotherapies, including the checkpoint inhibitors. Importantly, administration of varlilumab demonstrated minimal toxicity even in elderly patients. Treatment-related adverse events were infrequent and nearly all were mild to moderate in severity. The most common treatment-related adverse event observed across both arms was fatigue. Two isolated treatment-related serious adverse events were reported in the expansion cohorts—an episode of reversible bronchospasm in a patient with a history of these events, and a moderate infusion reaction that rapidly responded to standard treatment and did not prevent further varlilumab treatment. It is unclear whether these are a result of specific CD27 agonism.

Pharmacokinetic assessments conducted across both arms showed a dose-proportional exposure consistent with a human monoclonal antibody. Importantly, no significant anti-varlilumab antibodies were detected and consistent pharmacokinetics were observed through up to 5 cycles (14 months) of therapy. Varlilumab binding to its target CD27 was evident by sustained levels of varlilumab on circulating T cells and increased levels of soluble CD27.

Varlilumab was non-depleting and induced immunologic activity in patients that is consistent with both its mechanism of action and preclinical models. These included a rapid induction of pro-inflammatory cytokines, activation of T cells as assessed by increased HLA-DR expression and antigen specific responses. Varlilumab treatment was also associated with a marked decrease in regulatory T cells, which are associated with immunosuppressive activity.

Clinical Activity Overview:

In the lymphoid malignancies dose escalation arm (n=24) two patients are currently continuing treatment and have not yet been evaluated for response. As previously reported, a heavily pre-treated patient with aggressive Hodgkin lymphoma achieved a complete response (CR) after three cycles of varlilumab (0.3 mg/kg). She currently remains in remission at 12.9+ months. Six additional patients with Hodgkin lymphoma have been enrolled, the majority to the 10 mg/kg dose level, with one patient awaiting initial response evaluation. Three additional patients with non-Hodgkin lymphoma have experienced stable disease (SD) with a progression-free survival (PFS) range of 4.5 to 14 months. One of these patients experienced significant tumor shrinkage (36%).

As previously reported, all patients completed treatment in the solid tumor dose escalation arm (n=25). Four patients experienced SD with a PFS range of 3.0 to 22.4+ months. Patients enrolled in the expansion cohorts had metastatic disease and had progressed on prior therapies including checkpoint blockade, kinase inhibitor, and cytokine (IL-2 or IFN). In the melanoma expansion cohort (n=16), three patients have ongoing SD with a PFS range of 2.7+ to 11.5+ months, including a uveal melanoma patient with 12% shrinkage of measurable disease. In the renal cell carcinoma expansion cohort (n=15), one patient achieved a partial response (PR) at 2.7+ months; confirmatory scans are currently pending. Additionally, three patients have SD with a duration of 2.8+ to 8.4+ months. Five patients continue treatment, one of whom has not yet been seen for the first assessment of response.

Planned Combination Studies and Next Steps:

Celldex has generated laboratory data showing synergy when varlilumab is combined with other immune modulators, particularly checkpoint inhibitors but also standard chemotherapies. Considering the excellent safety profile and clear immune activation seen with varlilumab, Celldex plans to initiate multiple Phase 1/2 studies of varlilumab in combination with different anti-tumor approaches. These trials are intended to characterize the potential for varlilumab to augment efficacy in multiple settings and include evaluation of both low intermittent dosing and saturating dosing. The studies to date include:

- A Phase 1/2 simultaneous combination study of varlilumab with nivolumab in patients with melanoma, non-small cell lung cancer, colorectal, head and neck and ovarian cancers. These indications include those where nivolumab has shown clear efficacy, and others where observed activity has been more limited. The study will include a limited dose escalation phase, with subsequent parallel Phase 2 arms in each of these indications. A total of approximately 170 patients will be enrolled to evaluate immune and anti-tumor activity of the combination in multiple disease settings.
- A Phase 1/2 study of simultaneous varlilumab and Yervoy® in first- or second-line therapy for advanced melanoma. The Phase 2 portion will include up to 72 patients and will assess response rate and PFS. The trial will include CDX-1401 in up to 24 patients with NY-ESO+ metastatic melanoma. Immunological effects as well as any increase in anti-tumor effects will also be assessed in the patients treated with CDX-1401 to discern if CDX-1401 improves outcomes

in this subset of patients. Data from a Phase 1 study of CDX-1401 in solid tumors was recently published in *Science Translational Medicine* and suggested that CDX-1401 may predispose patients to better outcomes on subsequent therapy with checkpoint inhibitors. Eight patients completed the study and went on to receive subsequent therapy of either Yervoy® or an investigational checkpoint inhibitor and six of these patients had objective tumor regression (three metastatic melanoma PRs, two non-small cell lung cancer PRs and one metastatic melanoma CR). All six of the responding patients had tumors confirmed to express NY-ESO-1.

- A Phase 1/2 study of varlilumab plus the B-raf pathway targeted agents dabrafenib and trametinib (followed sequentially by a checkpoint inhibitor) for patients with B-raf mutated metastatic melanoma. Immunologic effects on melanoma specific antigens will be assessed at both low and high doses with a broader activity assessment from the direct combination in a Phase 2 portion. The effect of sequential varlilumab then commercial checkpoint inhibitor will be assessed as patients are followed for response and PFS through their next line of therapy.
- A Phase 1/2 study of varlilumab in combination with sunitinib in patients with advanced renal cell carcinoma. The potential for immunological and anti-tumor synergy between these agents will be assessed, noting the anti-tumor activity seen with varlilumab alone.

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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 Statements

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), varlilumab (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.

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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