Karyopharm Initiates Phase 1 Clinical Trial with KPT-9274

NEWTON, Mass., June 22, 2016 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), a clinical-stage pharmaceutical company, today announced dosing of the first patient in a Phase 1 clinical trial evaluating KPT-9274, an oral, first-in-class, dual-acting p21-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase (NAMPT) inhibitor, in patients with advanced solid malignancies (including sarcoma, colon and lung cancer) or non-Hodgkin's lymphoma (NHL) whose disease has relapsed after standard therapy(s) (NCT02702492).

This first-in-human, multi-center, open-label, dose-escalation trial is expected to enroll up to 175 patients. The primary endpoints of this study are to determine the recommended Phase 2 dose (RP2D) and the maximum tolerated dose (MTD) of KPT-9274 administered alone and with extended release niacin, and to evaluate safety and tolerability. The key secondary endpoint is to assess anti-tumor activity in patients predicted to be more sensitive to PAK4/NAMPT inhibition, including those with NAPRT-deficient tumors and tumors harboring IDH1 mutations.

"Our first-in-class, oral, small molecule PAK4 and NAMPT modulator, KPT-9274, has synergistic anti-tumor effects through several mechanisms including immune cell activation by inhibiting ß-catenin, reduction of NAD levels which tumor cells use as a key energy source, blockade of DNA damage repair mechanisms, and induction of tumor cell apoptosis," said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. "We are encouraged by the preclinical profile of KPT-9274, highlighted at the 2015 American Society of Hematology and 2016 American Association of Cancer Research annual meetings, which support the novel mechanism and demonstrated encouraging preclinical anti-tumor activity. To our knowledge, we are the only company with a compound in clinical development that directly targets both PAK4 and NAMPT. This important Phase 1 study will continue to build upon the body of scientific evidence supporting KPT-9274's safety and efficacy, and we look forward to reporting top-line data next year."

This Phase 1 clinical study is supported by extensive preclinical data demonstrating KPT-9274's anti-cancer activity against hematological and solid tumors while showing minimal toxicity to normal cells in vitro. Preclinical studies demonstrate that by blocking PAK4, KPT-9274 potently inhibits ß-catenin as well as certain Ras oncogene-dependent pathways. ß-catenin is believed to be a key mediator of immune suppression, including resistance to immune-activating therapies. In addition, both ß-catenin and Ras are key growth signaling pathways for many common tumors such as colon and lung cancers. NAMPT, which can be found in a complex with PAK4 within the cell, is a pleiotropic protein with intra- and extra-cellular functions as an enzyme, cytokine, growth factor and hormone, and is thought to play a role in cellular energy metabolism. Hematologic and solid tumor cells become dependent on both PAK4 and NAMPT pathways and are therefore susceptible to single-agent cytotoxicity by KPT-9274. In mouse and rat xenograft studies, orally administered KPT-9274 showed robust anti-cancer activity with favorable tolerability. Based on in vitro and in vivo activity, Karyopharm believes KPT-9274 holds significant potential for the treatment of a wide variety of both solid and hematological cancers.

About KPT-9274

KPT-9274 is a first-in-class, orally bioavailable, small molecule immunometabolic modulator that works through non-competitive dual inhibition of p21-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase (NAMPT). Co-inhibition of these targets is believed to lead to synergistic anti-tumor effects through suppression of ß-catenin by blocking PAK4, leading to both immune cell activation and inhibition of tumor growth, energy depletion through NAMPT inhibition, blockade of DNA repair, cell cycle arrest and ultimately apoptosis. KPT-9274 may therefore have both immune-activating and direct antitumor effects. In contrast, normal cells are less sensitive to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic demands.

About Karyopharm Therapeutics

Karyopharm Therapeutics Inc. (Nasdaq:KPTI) is a clinical-stage pharmaceutical company focused on the discovery and development of novel first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major diseases. Karyopharm's SINE™ compounds function by binding with and inhibiting the nuclear export protein XPO1 (or CRM1). In addition to single-agent and combination activity against a variety of human cancers, SINE™ compounds have also shown biological activity in models of neurodegeneration, inflammation, autoimmune disease, certain viruses and wound-healing. Karyopharm was founded by Dr. Sharon Shacham and is located in Newton, Massachusetts. For more information, please visit www.karyopharm.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the therapeutic potential of and potential clinical development plans for Karyopharm's drug candidates, including the timing of initiation of certain trials and of the reporting of data from such trials. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or

results to differ materially from the Company's current expectations. For example, there can be no guarantee that KPT-9274, or any of Karyopharm's SINE™ compounds, including selinexor (KPT-330) or any other drug candidate that Karyopharm is developing will successfully complete necessary preclinical and clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Karyopharm's ability to obtain and maintain requisite regulatory approvals and to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development of drug candidates by Karyopharm's competitors for diseases in which Karyopharm is currently developing its drug candidates; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, which was filed with the Securities and Exchange Commission (SEC) on May 9, 2016, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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