Karyopharm Therapeutics Presents Positive Clinical Data on the Activity of Selinexor in Combination with Other Anticancer Agents across Multiple Hematologic Malignancies at the 2015 American Society of Hematology (ASH) Annual Meeting

- Selinexor Demonstrates Promising Activity and Tolerability in Combination with Other Active Agents -
- Encouraging Efficacy and Tolerability Observed in Patients with Heavily Pretreated Refractory Myeloma and Relapsed/Refractory Acute Myeloid Leukemia -

NEWTON, Mass., Dec. 7, 2015 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), a clinical-stage pharmaceutical company, today announced the presentation of positive clinical and preclinical data describing the activity of its lead oncology drug candidate, selinexor, and its oncology pipeline for the treatment of hematologic malignancies at the 2015 American Society of Hematology (ASH) annual meeting held December 5-8, 2015 in Orlando, Florida. Oral and poster presentations representing both company and investigator-sponsored clinical and preclinical studies described data related to selinexor, Karyopharm's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE™) compound that inhibits exportin 1 (XPO1). In addition, encouraging preclinical data on other pipeline programs, including a second generation SINE™ compound, KPT-8602, and a dual acting p21-activated kinase 4 and nicotinamide phosphoribosyltransferase (PAK4/NAMPT) inhibitor, KPT-9274, were presented.

"Our investigators are highly encouraged by the activity of selinexor in combination with standard of care agents for the treatment of a variety of cancers," said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. "Data presented at ASH demonstrate that selinexor is efficacious and often synergistic in combination with other therapeutic agents, including carfilzomib and dexamethasone in refractory multiple myeloma, with Ara-C and idarubicin in relapsed or refractory acute myeloid leukemia (AML), and with fludarabine and cytarabine in pediatric patients with relapsed or refractory acute leukemias. These recent results add to the growing body of evidence seen with selinexor in combinations, including the recently announced preclinical synergy of selinexor with immune checkpoint inhibitors."

"In addition to selinexor, we continue to demonstrate Karyopharm's commitment and expertise in the field of SINE™ therapy with encouraging preclinical data presented for KPT-8602, a second generation SINE™ compound with distinct pharmaceutical properties and the potential for daily dosing. Exciting preclinical data was also presented at ASH for our novel, first-in-class, dual acting PAK4/NAMPT inhibitor," continued Dr. Shacham.

Selinexor in combination with standard of care agents in multiple myeloma

Preliminary data from an ongoing investigator sponsored trial (IST) of selinexor in combination with carfilzomib and dexamethasone in refractory multiple myeloma (MM) were previously presented at ASH 2014 and updated today with additional patient data. In light of these data presented by Andrzej Jakubowiak, MD, PhD, from The University of Chicago, with support from the Multiple Myeloma Research Consortium, Amgen Inc. and Karyopharm, Karyopharm plans to initiate a Phase 2/3 clinical study (SCORE) by early 2016 to evaluate the combination of selinexor, carfilzomib and dexamethasone versus carfilzomib and dexamethasone in patients with refractory MM who were previously treated with a proteasome inhibitor and an immunomodulatory agent. In addition, Karyopharm recently initiated a 3-arm Phase 1b/2 clinical study (STOMP) evaluating selinexor plus low dose dexamethasone in combination with the MM backbone therapies with either bortezomib or pomalidomide or lenalidomide. Karyopharm's commitment to these studies is based upon the growing body of preclinical evidence demonstrating that adding selinexor and dexamethasone to active anti-cancer agents, including proteasome inhibitors and immunomodulatory agents, may provide prolonged clinical benefit and restore drug sensitivity in MM.

"These data demonstrate encouraging efficacy of selinexor, carfilzomib and dexamethasone in heavily pretreated patients with highly refractory multiple myeloma, including patients whose disease is refractory to previous carfilzomib-based combinations, suggesting the potential of this combination to overcome carfilzomib resistance," said Dr. Andrzej J. Jakubowiak from The University of Chicago.

In a poster titled, "Phase 1 MMRC Trial of Selinexor, Carfilzomib (CFZ) and Dexamethasone (DEX) in Relapsed and Relapsed/Refractory Multiple Myeloma," Dr. Jakubowiak and his colleagues demonstrated a 67% overall response rate with the combination of selinexor, carfilzomib and dexamethasone and no unexpected toxicities observed to date. All evaluable patients whose responses were reported at ASH had MM that was refractory to carfilzomib.

- Nine patients with refractory MM were evaluable as of September 30, 2015, had a median age of 67 years and a median of four prior treatment regimens. All patients enrolled were refractory to prior carfilzomib-based treatment. Seven patients were carfilzomib-refractory in their last prior therapy before enrolling on the combination study with selinexor.

    - Response rates for all enrolled patients were 67% with partial responses (PR) or better, including 22% with very good partial responses (VGPR); 78% had at least minor responses (MR). Responses occurred rapidly within the first one to two cycles. Five of the seven (71%) patients refractory to carfilzomib in their last prior therapy responded with a PR or better.
    - Seven patients were evaluable for dose limiting toxicity (DLT) and no DLTs were reported. A maximum tolerated dose (MTD) has not yet been established, and none of the patients discontinued the study due to adverse events (AEs). The AEs were reversible and manageable with supportive care. Grade 3/4 AEs were predominantly hematological and included thrombocytopenia (67%), neutropenia (44%), lymphopenia (22%) and anemia (22%). The most common grade 3/4 non-hematologic AE was fatigue (22%).

Additionally, in two posters titled, "Selinexor is an Effective Cancer Treatment in Hypoxic Conditions and Synergizes with Proteasome Inhibitors to Treat Drug Resistant Multiple Myeloma," and "Combination Therapy of Selinexor with Bortezomib or Carfilzomib Overcomes Drug Resistance to Proteasome Inhibitors (PI) in Human Multiple Myeloma," Karyopharm researchers and collaborators demonstrated the potential of selinexor to synergize with proteasome inhibitors to overcome drug resistance.

Selinexor combinations in acute myeloid leukemia (AML)

Clinical data presented at ASH demonstrated the activity and tolerability of selinexor in combination with standard of care agents in the AML setting; a Phase 2 trial investigating the efficacy and tolerability of arabinoside cytosine (Ara-C) and idarubicin in combination with selinexor in "fit" patients with relapsed and/or refractory AML and a Phase 1 study determining the safety and efficacy of selinexor in combination with fludarabine and cytarabine in pediatric patients with relapsed and/or refractory acute leukemia.

"Acute myeloid leukemia is the most frequent cause of leukemia-related death. While complete response rates can be as high as 80% in patients undergoing initial induction chemotherapy, the majority of AML patients will relapse with a bleak prognosis. As there is currently no standard-of-care regimen for these patients, a great unmet medical need exists for new treatment options such as selinexor," said Walter Fiedler, MD of the University Medical Center Hamburg-Eppendorf, Germany, the lead investigator for the study.

In a poster titled, "SAIL: Selinexor, ARA-C and Idarubicin: An Effective and Tolerable Combination in Patients with Relapsed/Refractory AML: A Multicenter Phase II Study," Karyopharm researchers in collaboration with Dr. Fiedler demonstrated that Ara-C and idarubicin in combination with selinexor has the potential to achieve significant response rates, particularly in this heavily pretreated patient population, without unexpected toxicities observed to date. Importantly, these responses enabled the majority of patients to proceed to allogeneic stem cell transplantation.

- As of June 16, 2015, 20 patients with relapsed/refractory AML were evaluable for efficacy and toxicity. Median age was 59 (range 22-78) years. On average, patients received approximately 3.5 (range 1-6) prior therapies, all including intensive chemotherapy.
- Overall response rate (ORR) was 60% (45% of patients achieved complete response (CR), 5% of patients achieved complete response with incomplete count recovery (CRi) and 10% of patients achieved PR). Sixty percent of patients treated received or were planned for stem cell transplantation or donor lymphocyte infusion.
- The most frequent non-hematologic AEs were vomiting, diarrhea, nausea, fatigue, anorexia and neutropenic fever. One treatment-related death occurred wherein a patient with grade 4 thrombocytopenia developed a subarachnoid hemorrhage, which is common in relapsed AML due to intensive chemotherapy and is a less frequent consequence of single-agent selinexor treatment.

This trial will be expanded further, and has provided the basis for several front-line and other combination therapies for the treatment of AML.

In a poster titled "Phase I Study of Selinexor, a Selective Inhibitor of Nuclear Export, in Combination with Fludarabine and Cytarabine (AraC) in Pediatric Patients with Relapsed or Refractory Leukemia," Karyopharm

researchers in collaboration with Jeffrey E. Rubnitz, MD of St. Jude Children's Research Hospital demonstrated that selinexor given in combination with fludarabine and cytarabine is tolerable in pediatric patients with relapsed acute leukemia. Most patients demonstrated XPO1 target inhibition with encouraging response rates which will be further explored in the Phase 2 portion of this trial.

- Eighteen children or adolescents with relapsed or refractory acute leukemia (prior therapies included intensive chemotherapy combinations) completed at least one cycle of selinexor and were evaluable for safety; four treated at dose level 1 (30 mg/m2), three at dose level 2 (40 mg/m2), six at dose level 3 (55 mg/m2), and five at dose level 4 (70 mg/m2). Two DLTs of cerebellar toxicity were observed at dose level 4 (70 mg/m2), thereby establishing a maximum tolerated dose (MTD) of 55 mg/m2. The most common grade 3 or 4 non-hematologic toxicity related to selinexor was asymptomatic hyponatremia, which was observed in 13 patients and easily corrected in all cases.
- Twelve patients were evaluable for response. The ORR was 67%. Four patients achieved CR, 2 CRi, and two had a PR. Seven of the eight patients with objective responses underwent subsequent stem cell transplantation.
- Inhibition of XPO1 was assessed by quantitative real-time polymerase chain reaction, or qRT-PCR, of XPO1 mRNA, which is upregulated in response to selinexor. Thirteen of the first fourteen patients enrolled on the trial demonstrated at least two-fold induction of XPO1 mRNA, which persisted for at least 48 hours, indicating prolonged inhibition of the protein by selinexor.

Optimizing selinexor dose

Karyopharm researchers also presented data establishing 60mg as the most appropriate selinexor dose for both efficacy and tolerability across many of the hematologic cancers as well as preclinical data on Karyopharm's emerging oncology pipeline including KPT-8602, a second generation SINE™ compound, and KPT-9274, Karyopharm's novel, first-in-class, dual acting PAK4/NAMPT inhibitor.

In an oral presentation titled, "Safety, Efficacy, and Determination of the Recommended Phase 2 Dose for the Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330)," Karyopharm researchers and Christine Chen, MD, of the Princess Margaret Cancer Center demonstrated that while efficacy was comparable, doses of selinexor from 45-65mg (median 60mg) were better tolerated than doses greater than 65mg and showed less weight loss, fewer incidence of high grade adverse events, and greater numbers of days on study.

- 266 heavily pretreated patients with MM, non-Hodgkin's lymphoma, AML, and other hematological malignancies were divided into three groups of evaluable patients: those that received 4-44mg (median 30mg), 45-65mg (median 60mg) and &#62 65mg (70-160mg; median 90mg) for comparison of safety and efficacy endpoints.
- Patients in the 4-44mg and 45-65mg groups remained on study longer than those receiving &#62 65mg, with average treatment duration of 120 days versus 90 days, respectively. Overall efficacy appeared superior in the 45-65mg dose group across multiple hematologic indications.
- The most common AEs were nausea (63%), fatigue (62%), anorexia (57%), vomiting (38%), which were mostly grade 1/2, and thrombocytopenia (41%), which was mostly grade 3/4, but with very low rates of bleeding. The incidence of certain selinexor-related high grade (3/4) AEs was less in patients receiving 45-65mg selinexor vs those receiving &#62 65mg.

These data from Karyopharm's extensive Phase 1 selinexor experience with selinexor corroborate our findings that a flat dose of 60mg is the most appropriate selinexor dose for both efficacy and tolerability in several settings, including older patients with AML. However, as is the case for many other anti-cancer drugs, certain indications will be treated with different doses.

Karyopharm's new oncology pipeline candidates

In two oral presentations titled, "Nuclear Export Inhibitor KPT-8602 is Highly Active Against Leukemic Blasts and Leukemia-Initiating Cells in Patient-Derived Xenograft Models of AML" and "Next Generation XPO1 Inhibitor Shows Improved Efficacy and In Vivo Tolerability in Hematologic Malignancies" and a poster titled "Next Generation XPO1 Inhibitor KPT-8602 for the Treatment of Drug-Resistant Multiple Myeloma," Karyopharm researchers and collaborators demonstrated the potential of this second generation SINE™ compound for higher and/or more frequent dosing with KPT-8602 compared with selinexor. Based on these data, Karyopharm plans to initiate a focused Phase 1 MM study with KPT-8602 in the first quarter of 2016.

Finally, in two posters titled, "In Vitro and In Vivo Anti-Leukemic Effects of PAK4 Allosteric Modulators in Acute Myeloid Leukemia: Promising Results Justifying Further Development" and "Dissecting Signaling Network Responses to PAK4 Allosteric Modulators in Cell Subsets within Primary Human Acute Myeloid Leukemia Samples," encouraging preclinical activity was reported with KPT-9274 (PAK4/NAMPT inhibitor) and based on these data, Karyopharm plans to initiate clinical development in patients with heavily pretreated solid tumors or

lymphoma in the first half of 2016.

Selinexor single-agent hematologic studies enrollment updates

Karyopharm is actively enrolling patients in four later phase clinical studies evaluating single-agent selinexor: one in older patients with relapsed/refractory AML (SOPRA study), the second in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (SADAL study), the third in patients with MM (STORM study) and the fourth in patients with Richter's transformation (SIRRT study). Interim data are expected from the SOPRA and STORM studies in the middle of 2016. In conjunction with discussions with the U.S. Food and Drug Administration (FDA), Karyopharm has amended the protocol for its ongoing Selinexor Against Diffuse Aggressive Lymphoma (SADAL) study in patients with heavily pretreated DLBCL to remove dexamethasone from the regimen and evaluate selinexor as a single-agent in this patient population and to adjust SADAL's inclusion and exclusion criteria. The study will continue to compare 60mg and 100mg twice weekly doses of selinexor with 100 patients per arm. Based on these amendments, the company expects to report top-line data from this study in the first quarter of 2017.

About selinexor

Selinexor (KPT-330) is a first-in-class, oral Selective Inhibitor of Nuclear Export (SINE™) compound. Selinexor functions by binding to and inhibiting the nuclear export protein XPO1 (also called CRM1), leading to the accumulation of tumor suppressor proteins in the cell nucleus. This reinitiates and amplifies their tumor suppressor function and is believed to lead to the selective induction of apoptosis in cancer cells, while largely sparing normal cells. Over 1,300 patients have been treated with selinexor in company and investigator-sponsored Phase 1 and Phase 2 clinical trials in advanced hematologic malignancies and solid tumors. Karyopharm has initiated four later-phase clinical trials of selinexor, including one in older patients with AML (SOPRA), one in patients with Richter's transformation (SIRRT), one in patients with DLBCL (SADAL) and a single-arm trial of selinexor and lose-dose dexamethasone in patients with MM (STORM). Karyopharm plans to initiate a Phase 2/3 clinical study (SCORE) in early 2016 to evaluate the combination of selinexor, carfilzomib and dexamethasone versus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma who were previously treated with a proteasome inhibitor and an immunomodulatory drug. In solid tumors, Karyopharm plans to initiate a randomized, placebo-controlled Phase 2/3 trial of selinexor to treat liposarcoma during the fourth quarter of 2015. Additional Phase 1 and Phase 2 studies are ongoing or currently planned, including multiple studies in combination with one or more approved therapies in a variety of tumor types to further inform the company's clinical development priorities for selinexor. The latest clinical trial information for selinexor is available at www.clinicaltrials.gov.

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 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 activity against a variety of human cancers, SINE™ compounds have also shown biological activity in models of 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 any of Karyopharm's SINE™ compounds, including selinexor (KPT-330), KPT-8602, Karyopharm's next generation SINE™ compound, or KPT-9274, Karyopharm's novel, first-in-class, dual acting PAK4/NAMPT inhibitor, 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 September 30, 2015, which is on file with the Securities and Exchange Commission (SEC) as of November 9, 2015, 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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