Karyopharm Announces Publication of XPOVIO® (Selinexor) Phase 2b SADAL Study Results in The Lancet Haematology

NEWTON, Mass., June 24, 2020 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), an innovation-driven pharmaceutical company, today announced that the results of the Phase 2b SADAL (Selinexor Against Diffuse Aggressive Lymphoma) study evaluating XPOVIO in patients with relapsed or refractory diffuse large B-cell lymphoma (RR DLBCL) were published online in The Lancet Haematology. The SADAL study evaluated selinexor, the Company's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound for the treatment of adult patients with RR DLBCL, not otherwise specified, who have received at least two prior therapies.

"The clinical outcomes for patients with heavily pretreated relapsed or refractory DLBCL are typically very poor, and hence results from the multinational Phase 2b SADAL study are noteworthy," said Prof Nagesh Kalakonda, University of Liverpool, lead author of the manuscript. "In this population, single-agent oral XPOVIO (selinexor) demonstrated an overall response rate of 28%, including a complete response rate of 12%. Responses were seen in all subgroups regardless of age, gender, prior therapy, DLBCL subtype or prior stem cell transplant therapy. Importantly, patient responses were durable with a median duration of response of 9.3 months (23.0 months for patients who achieved a complete response). Finally, responses were associated with longer survival, underscoring the potential of oral XPO1 inhibition as an oral, non-chemotherapeutic option for patients with RR DLBCL."

"These positive data further reinforce our strong belief that oral XPOVIO offers patients an important new treatment option, especially considering the patient population studied in SADAL had an expected median survival of less than six months. Furthermore, treatment with XPOVIO demonstrated deep and durable responses with a safety profile qualitatively similar to previous clinical studies with XPOVIO," said Sharon Shacham, PhD, MBA, Founder, President and Chief Scientific Officer of Karyopharm. "We are proud to see these published clinical results and are excited to now commercialize XPOVIO in our second cancer indication on behalf of the patients and families who are desperately in need of new treatment options."

The U.S. Food and Drug Administration (FDA) approved XPOVIO on June 22, 2020 for the treatment of adult patients with RR DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. This indication was approved based on response rate under the FDA's Accelerated Approval Program, which was developed to allow for expedited approval of drugs that treat serious conditions and that fill an unmet medical need. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). A Marketing Authorization Application for selinexor for RR DLBCL is planned for submission to the European Medicines Agency in 2021.

The Phase 2b SADAL Study Results

The published results are based on the multi-center, single-arm Phase 2b SADAL study (NCT02227251), which evaluated 127 patients (median of 2 prior treatment regimens) with RR DLBCL. Patients received a fixed 60 mg dose of XPOVIO given orally twice weekly for a four-week cycle. Patients with germinal center B-cell (GCB) or non-GCB subtypes of DLBCL were included in enrollment.

The SADAL study met its primary endpoint of overall response rate (ORR) with an ORR of 28%, including 15 complete responses (CRs) and 21 partial responses (PRs). An additional 11 patients experienced stable disease (SD) for a disease control rate of 37.0%. The ORR in the 59 patients with the GCB-subtype was 34% and the ORR in the 63 patients with the non-GCB subtype was 21%. In addition, there were 5 patients enrolled whose subtype was unclassified and 1 of these patients achieved a CR while 2 of these patients achieved a partial response (PR).

Key secondary endpoints included a median duration of response (DOR) in the responding patients of 9.3 months and median overall survival (OS) across the entire study population of 9.1 months. Median OS has not yet been reached in patients who achieved either a CR or PR. In patients who had stable disease, the median OS was 18.3 months. Patients whose disease progressed or had no response to XPOVIO had a median OS of 4.3 months, which is consistent with the expected poor prognosis for patients who have RR DLBCL and have been previously treated with two or more lines of therapy.

All 127 patients were included in the safety analyses. The most common treatment-related adverse events (AEs) were cytopenias along with gastrointestinal and constitutional symptoms and were generally reversible and managed with dose modifications and/or standard supportive care. The most common non-hematologic AEs were nausea (58%), fatigue (47%), and decreased appetite (37%) and were mostly Grade 1 and 2 events. As expected, the most common Grade 3 and 4 AEs were thrombocytopenia (46%), neutropenia (24%) and anemia (22%) and were generally not associated with clinical sequelae.

The patient population described in this publication includes data from 127 patients in the SADAL study while the FDA approved label includes data from seven additional patients or 134 patients total. As such, there are minor differences in the efficacy and safety percentages between the two sources.

About XPOVIO® (selinexor)

XPOVIO is a first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound. XPOVIO functions by selectively binding to and inhibiting the nuclear export protein exportin 1 (XPO1, also called CRM1). XPOVIO blocks the nuclear export of tumor suppressor, growth regulatory and anti-inflammatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. The forced nuclear retention of these proteins can counteract a multitude of the oncogenic pathways that, unchecked, allow cancer cells with severe DNA damage to continue to grow and divide in an unrestrained fashion. Karyopharm received accelerated U.S. Food and Drug Administration (FDA) approval of XPOVIO in July 2019 in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Karyopharm has also submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) with a request for conditional approval of selinexor in this same RRMM indication. Karyopharm submitted a supplemental New Drug Application (sNDA) to the FDA requesting an expansion of its current indication to include the treatment for patients with multiple myeloma after at least one prior line of therapy based on the positive results from the Phase 3 BOSTON study which evaluated selinexor in combination with Velcade® (bortezomib) and low-dose dexamethasone. In June 2020, Karyopharm received accelerated FDA approval of XPOVIO for its second indication in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. Selinexor is also being evaluated in several other mid-and later-phase clinical trials across multiple cancer indications, including as a potential backbone therapy in combination with approved myeloma therapies (STOMP), in liposarcoma (SEAL) and in endometrial cancer (SIENDO), among others. Additional Phase 1, Phase 2 and Phase 3 studies are ongoing or currently planned, including multiple studies in combination with approved therapies in a variety of tumor types to further inform Karyopharm's clinical development priorities for selinexor. Additional clinical trial information for selinexor is available at www.clinicaltrials.gov.

For more information about Karyopharm's products or clinical trials, please contact the Medical Information department at:

Tel: +1 (888) 209-9326
Email: medicalinformation@karyopharm.com

IMPORTANT SAFETY INFORMATION

Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma (MM) and developed or worsened in patients with DLBCL.

Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia: XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection. Neutropenia and febrile neutropenia occurred in patients with MM and in patients with DLBCL.

Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction (AR).

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients with MM and DLBCL.

Nausea/Vomiting: Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose, or permanently discontinue based on severity of ARs. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea: Interrupt, reduce dose, or permanently discontinue based on severity of ARs. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration, and replace electrolytes as clinically indicated.

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Interrupt, reduce dose, or permanently discontinue based on severity of ARs. Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia. Hyponatremia developed in patients with MM and in patients with DLBCL.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first 2 months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose, or permanently discontinue based on severity of the AR.

Serious Infection: XPOVIO can cause serious and fatal infections. Most infections were not associated with Grade 3 or higher neutropenia. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Monitor for signs and symptoms of infection, and evaluate and treat promptly.

Neurological Toxicity: XPOVIO can cause life-threatening neurological toxicities.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

Embryo-Fetal Toxicity: XPOVIO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (ARs) in ≥20% of patients with MM are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The most common ARs, excluding laboratory abnormalities, in ≥20% of patients with DLBCL are fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3-4 laboratory abnormalities in ≥15% of patients included thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. Grade 4 laboratory abnormalities in ≥5% were thrombocytopenia, lymphopenia, and neutropenia.

In patients with MM, fatal ARs occurred in 9% of patients. Serious ARs occurred in 58% of patients. Treatment discontinuation rate due to ARs was 27%. The most frequent ARs requiring permanent discontinuation in ≥4% of patients included fatigue, nausea, and thrombocytopenia.

In patients with DLBCL, fatal ARs occurred in 3.7% of patients within 30 days, and 5% of patients within 60 days of last treatment; the most frequent fatal AR was infection (4.5% of patients). Serious ARs occurred in 46% of patients; the most frequent serious AR was infection. Discontinuation due to ARs occurred in 17% of patients.

USE IN SPECIFIC POPULATIONS

In MM, no overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥75 years old had a higher incidence of discontinuation due to an AR than younger patients, a higher incidence of serious ARs, and a higher incidence of fatal ARs.

Clinical studies in patients with relapsed or refractory DLBCL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on XPOVIO pharmacokinetics is unknown.

Please see full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

About Karyopharm Therapeutics

Karyopharm Therapeutics Inc. (Nasdaq: KPTI) is an innovation-driven pharmaceutical company dedicated to the discovery, development, and commercialization of novel first-in-class drugs directed against nuclear export and related targets for the treatment of cancer and other major diseases. Karyopharm's Selective Inhibitor of Nuclear Export (SINE) compounds function by binding with and inhibiting the nuclear export protein XPO1 (or CRM1). Karyopharm’s lead compound, XPOVIO® (selinexor), received accelerated approval from the U.S. Food and Drug Administration (FDA) in July 2019 in combination with dexamethasone as a treatment for patients with heavily pretreated multiple myeloma. In June 2020, XPOVIO was approved by the FDA as a treatment for patients with relapsed or refractory diffuse large B-cell lymphoma. A Marketing Authorization Application for selinexor for patients with heavily pretreated multiple myeloma is also currently under review by the European Medicines Agency. 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 has several investigational programs in clinical or preclinical development. 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 Karyopharm’s beliefs regarding XPOVIO’s ability to treat patients with relapsed or refractory diffuse large B-cell lymphoma and expectations related to other XPOVIO regulatory submissions. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that any positive developments in the development or commercialization of 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: the risk that the COVID-19 pandemic could disrupt Karyopharm’s business more severely than it currently anticipates, including by reducing sales of XPOVIO, interrupting or delaying research and development efforts, impacting the ability to procure sufficient supply for the development and commercialization of selinexor or other product candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm’s drug candidates that receive regulatory approval; the ability to retain regulatory approval of XPOVIO or any of Karyopharm’s drug candidates that receive regulatory approval; 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, including with respect to the need for additional clinical studies; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; 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 indications 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, 2020, which was filed with the Securities and Exchange Commission (SEC) on May 5, 2020, 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, except as required by law, Karyopharm expressly disclaims any obligation to update any forward-looking statements,

whether as a result of new information, future events or otherwise.

Velcade® is a registered trademark of Takeda Pharmaceutical Company Limited.

Contacts:

Investors:
Karyopharm Therapeutics Inc.
Ian Karp, Vice President, Investor and Public Relations
857-297-2241 | ikarp@karyopharm.com

Media:

FTI Consulting
Simona Kormanikova or Robert Stanislaro
212-850-5600 | Simona.Kormanikova@fticonsulting.com or robert.stanislaro@fticonsulting.com

Source: Karyopharm Therapeutics Inc.