Karyopharm Announces FDA Approval of XPOVIO® (Selinexor) as a Treatment for Patients with Multiple Myeloma After At Least One Prior Therapy

-- Oral XPOVIO Now Available as a Treatment Option for Patients with Multiple Myeloma As Early as First Relapse; Significantly Expands Addressable Patient Population --
-- Oral XPOVIO is Now the Only Multiple Myeloma Drug Indicated as Part of an Approved, Once-Weekly Velcade® (bortezomib) Combination Regimen --
-- First Multiple Myeloma Drug with a New Mechanism of Action Approved by the FDA in the Second-Line Setting Since 2016 -
-- FDA Approval Comes Approximately Three Months Ahead of Target PDUFA Date --
-- Karyopharm to Hold an Investor Conference Call and Webcast Today at 1:00 p.m. ET --

NEWTON, Mass., Dec. 18, 2020 /PRNewswire/ -- Karyopharm Therapeutics Inc. (Nasdaq: KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, today announced that the U.S. Food and Drug Administration (FDA) has approved XPOVIO® (selinexor), the Company's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) medicine, in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. XPOVIO was previously approved under the FDA's Accelerated Approval Program for the treatment of adult patients with relapsed or refractory multiple myeloma 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.

"Today's U.S. approval broadens the existing label for XPOVIO and allows Karyopharm to offer a new, highly active, treatment option to a significantly expanded patient population," said Sharon Shacham, PhD, MBA, Founder, President and Chief Scientific Officer of Karyopharm. "We believe the expanded reach of XPOVIO will address a critical need for patients with multiple myeloma given its novel mechanism of action, convenient oral administration and established rapid and sustained efficacy profile. The XPOVIO label expansion approval was supported by the pivotal Phase 3 BOSTON study, which was recently published in *The Lancet.* This approval was made possible by the patients, caregivers and physicians who participated in the clinical development of XPOVIO, as well as our global, dedicated Karyopharm team that has worked tirelessly to advance this innovative therapy to the greater multiple myeloma community."

"New treatments for multiple myeloma remain a critical need for both patients and their treating physicians," saidPaul Richardson, MD, Clinical Program Leader and Director of Clinical Research, Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute and co-senior author of the BOSTON study publication. "Selinexor with once weekly bortezomib-dexamethasone (SVd) demonstrated encouraging and highly significant results in the Phase 3 BOSTON study, including a 47% improvement in progression-free survival versus standard twice weekly bortezomib-dexamethasone (Vd). Patients receiving SVd had approximately 35% fewer clinic visits compared to those receiving the standard, twice-weekly Vd regimen, thus receiving 40% less bortezomib and 25% less dexamethasone as compared with the control arm in the first 24 weeks of therapy. This once-weekly dosing feature helps makes the SVd regimen attractively simple. Importantly, patients achieved a significantly higher overall response of 76% with once-weekly SVd compared with the standard control arm therapy, and higher response rates were observed regardless of prior therapies received, the presence of high-risk cytogenetics, renal impairment or advanced age. Finally, adverse events with SVd were important but generally self-limiting, reversible, and proved manageable with dose modifications and aggressive supportive care, as well as generating significantly lower rates of peripheral neuropathy compared to the control group. As the only approved nuclear export inhibitor that has demonstrated a strong synergistic effect with a proteasome inhibitor such as bortezomib, selinexor has, in my opinion, the potential to meet a current treatment gap for our multiple myeloma patients in need of new therapeutic options."

"We plan to immediately launch XPOVIO in this earlier-line indication by leveraging our established commercial infrastructure and growing account base of academic institutions and community-based oncology practices," said Michael G. Kauffman, MD, PhD, Chief Executive Officer of Karyopharm. "In parallel to our commercial initiatives in the U.S., we continue to collaborate with the European Medicines Agency (EMA) on the Marketing Authorization Application (MAA) of XPOVIO with the goal of further growing the global reach of XPOVIO to more patients in need."

In addition to multiple myeloma, XPOVIO is also approved for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy.

About the Phase 3 BOSTON Study

The FDA approval of XPOVIO's expanded indication is supported by the results of the BOSTON study, a multi-center, Phase 3, randomized study (NCT03110562), which evaluated 402 adult patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. The study was designed to compare the efficacy, safety and certain health-related quality of life parameters of once-weekly XPOVIO (selinexor) in combination with once-weekly Velcade® (bortezomib) plus low-dose dexamethasone (SVd) versus twice-weekly Velcade® plus dexamethasone (Vd). The primary endpoint of the study was progression-free survival (PFS) and key secondary endpoints included overall response rate (ORR), rate of peripheral neuropathy, and others. Additionally, the BOSTON study allowed for patients on the Vd control arm to crossover to the SVd arm following objective (quantitative) progression of disease verified by an Independent Review Committee (IRC). The BOSTON study was conducted at over 150 clinical sites internationally.

Although the study had one of the highest proportions of patients with high-risk cytogenetics (~50%) as compared with other Velcade-based studies in previously treated multiple myeloma, the median PFS in the SVd arm was 13.9 months compared to 9.5 months in the Vd arm, representing a 4.4 month (47%) increase in median PFS (hazard ratio of 0.70; p=0.0075). The SVd arm also demonstrated a significantly greater ORR compared to the Vd arm (76.4% vs. 62.3%, p=0.0012). Importantly, SVd therapy compared to Vd therapy showed consistent PFS benefit and higher ORR across several important subgroups.

In addition, the following results favored SVd therapy as compared to Vd therapy:

- SVd therapy demonstrated a significantly higher rate of deep responses, defined as ≥ Very Good Partial Response compared to Vd therapy (44.6% vs. 32.4%) as well as a longer median duration of response (20.3 months vs. 12.9 months). Additionally, 17% of patients on the SVd arm achieved a Complete Response or a Stringent Complete Response as compared to 10% of patients receiving Vd therapy. All responses were confirmed by an IRC.
- Peripheral neuropathy (PN) rates were significantly lower on SVd compared to Vd (32% vs. 47%). In addition, PN rates ≥ Grade 2 were also significantly lower in the SVd arm compared to the Vd arm (21% vs. 34%).

The most common adverse reactions were cytopenias, along with gastrointestinal and constitutional symptoms and were consistent with those previously reported from other selinexor studies. Most adverse reactions were manageable with dose modifications and/or standard supportive care. The most common non-hematologic adverse reactions were fatigue (59%), nausea (50%), decreased appetite (35%), and diarrhea (32%) and were mostly Grade 1 and 2 events. The most common Grade 3 and 4 adverse reactions were thrombocytopenia (43%), lymphopenia (38%), fatigue (28%) and anemia (17%).

The full results from the BOSTON study were recently published in *The Lancet* and can be found **here**.

Conference Call Information

Karyopharm will host a conference call today, Friday, December 18, 2020, at 1:00 p.m. Eastern Time, to discuss the FDA's approval of the expanded XPOVIO label. To access the conference call, please dial (877) 870-4263 (local) or (412) 317-0790 (international) at least 10 minutes prior to the start time and ask to be joined into the Karyopharm Therapeutics call. A live audio webcast of the call will be available under "Events & Presentations" in the Investor section of the Company's website, http://investors.karyopharm.com/events-presentations. An archived webcast will be available on the Company's website approximately two hours after the event.

About Multiple Myeloma

According to the National Cancer Institute (NCI), multiple myeloma is one of the most common types of blood cancer in the U.S. with more than 32,000 new cases each year and over 140,000 patients living with the disease. It is most frequently diagnosed among people aged 65-74 years old. Despite recent therapeutic advances, there is currently no cure and most patients' disease will typically progress following treatment with currently available therapies. According to the NCI, nearly 13,000 deaths due to multiple myeloma are expected in the U.S. in 2020.

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's supplemental New Drug Application (sNDA) requesting an expansion of its indication to include the treatment for patients with multiple myeloma after at least one prior therapy was approved by the FDA on December 18, 2020. 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.

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. Monitor patients for signs and symptoms of bleeding. 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.

Monitor more frequently during the first 3 months of treatment. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients.

Nausea/Vomiting/Diarrhea: Provide prophylactic antiemetics or treatment as needed.

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia.

Monitor sodium level at baseline and throughout treatment.

Serious Infection: XPOVIO can cause serious and fatal infections. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

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 until the neurological toxicity fully resolves. 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.

Cataracts: New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataract requiring clinical intervention was reported.

ADVERSE REACTIONS

The most common adverse reactions (ARs) (≥20%) in patients with multiple myeloma who received SVd were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract, and vomiting.

Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Fatal ARs occurred in 6% of patients within 30 days of last treatment. Serious ARs occurred in 52% of patients. Treatment discontinuation rate due to ARs was 19%. The most frequent ARs requiring permanent discontinuation in >2% of patients included fatigue, nausea, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

USE IN SPECIFIC POPULATIONS

No overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥65 years old had a higher incidence of discontinuation due to an adverse reaction (AR) and a higher incidence of serious ARs than younger patients.

The effect of end-stage renal disease (CL_{CR} <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 a commercial-stage pharmaceutical company pioneering novel cancer therapies and 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 and in December 2020 in combination with Velcade® (bortezomib) and dexamethasone as a treatment for patients with multiple myeloma after at least one prior therapy. 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 expectations and plans relating to XPOVIO for the treatment of patients with relapsed or refractory multiple myeloma or relapsed or refractory diffuse large B-cell lymphoma; commercialization of XPOVIO or any of its drug candidates and the commercial performance of XPOVIO; submissions to, and the review and potential approval of selinexor by, regulatory authorities, including the Company's regulatory strategy, the anticipated availability of data to support such submissions, timing of such submissions and actions by regulatory authorities and the potential availability of accelerated approval pathways; the expected design of the Company's clinical trials; and the therapeutic potential of and potential clinical development plans for Karyopharm's drug candidates, especially selinexor. 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 Karyopharm will successfully commercialize XPOVIO; that regulators will agree that selinexor qualifies for conditional approval in the European Union as a result of data from the STORM study or confirmatory approval in the European Union based on the BOSTON study in patients with multiple myeloma; or that any of Karyopharm's drug candidates, including selinexor, will successfully complete necessary 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 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 negatively impacting 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 or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any

product or product candidate. 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, 2020, which was filed with the Securities and Exchange Commission (SEC) on November 2, 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.

XPOVIO®(selinexor) is a registered trademark of Karyopharm Therapeutics Inc. Velcade® is a registered trademark of Takeda Pharmaceutical Company Limited.

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