# Karyopharm Announces Publication of XPOVIO® (Selinexor) Phase 3 BOSTON Study Results in The Lancet

NEWTON, Mass., Nov. 12, 2020 /PRNewswire/ -- Karyopharm Therapeutics Inc. (Nasdaq: KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, today announced that the results of the Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study evaluating XPOVIO in patients with relapsed or refractory multiple myeloma were published online in *The Lancet*. The BOSTON study evaluated once weekly XPOVIO, the Company's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound, in combination with *once weekly* Velcade® (bortezomib) and low-dose dexamethasone against standard *twice weekly* Velcade in adult patients with multiple myeloma who had received one to three prior lines of therapy.

"The results from the BOSTON study published in *The Lancet* demonstrate that the once-weekly regimen of XPOVIO and Velcade®, with low-dose dexamethasone (SVd) reduced the risk of disease progression or death by 30% and induced a higher rate of overall and deep responses compared to patients receiving a standard twice-weekly Velcade® and low-dose dexamethasone regimen (Vd). This was observed despite approximately 40% less Velcade®, 25% less dexamethasone and approximately 35% fewer clinic visits on the SVd arm as compared with the standard Vd therapy arm. Encouragingly, the efficacy of the SVd regimen was consistent and noteworthy across several key subgroups, including patients who were frail or 65 years and older, patients with high-risk cytogenetics, patients with moderate renal impairment and patients who had either prior bortezomib or lenalidomide treatment," said Dr. Paul Richardson, MD, Clinical Program Leader and Director of Clinical Research, Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute and co-senior author of the manuscript.

"Despite the enrollment of 50% of patients with high risk cytogenetics, a particularly difficult to treat population, the SVd regimen demonstrated a 47% improvement in progression-free survival as compared to the Vd regimen and an overall response rate of 76.4%. Additionally, the rate and severity of peripheral neuropathy, a key treatment-limiting side effect commonly seen with Velcade® therapy, was significantly lower on the SVd arm compared to the Vd arm and may lead to improved patient quality of life," said Sundar Jagannath, MD, Director of the Center of Excellence for Multiple Myeloma and Professor of Medicine, Hematology and Medical Oncology, at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai, and an investigator in the BOSTON study.

"We are honored to have the Phase 3 BOSTON data selected for publication in such a highly esteemed medical journal and to be shared with the global oncology community," said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. "We believe the successful outcome of this study represents an important advancement for myeloma patients and we are sincerely grateful to all of the patients and investigators who participated in the BOSTON study. While XPOVIO received accelerated FDA approval last year for patients with penta-refractory multiple myeloma, a supplemental New Drug Application requesting approval for XPOVIO as a treatment for patients with multiple myeloma who have received one prior line of therapy has been accepted by the FDA and assigned a PDUFA action date of March 19, 2021. We are working closely with the regulatory authorities in both the U.S. and Europe to make this potential new treatment option, with a completely novel mechanism of action, available to patients as quickly as possible, if approved."

Once-weekly SVd is a novel, effective and convenient triplet therapy that utilizes approximately 40% less Velcade® and 25% less dexamethasone and requires approximately 35% fewer clinic visits during the first 24 weeks of treatment compared to the standard Vd regimen. Because Velcade® is given as a subcutaneous injection rather than as an infusion, clinic visits may be shorter with the SVd regimen than with other non-Velcade® regimens that may be employed to treat relapsed multiple myeloma and require intravenous infusions.

**The Phase 3 BOSTON Study Results as Published in the Lancet**

The published BOSTON study results are based on the 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 selinexor in combination with once-weekly Velcade® (bortezomib) plus low-dose dexamethasone (SVd) versus twice-weekly Velcade® plus low-dose 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 myeloma, the median PFS in the SVd arm was 13.93 months compared to 9.46 months in the Vd arm, representing a 4.47 month (47%) increase in median PFS (hazard ratio[HR]=0.70; p=0.0075). The SVd group also demonstrated a significantly greater ORR compared to the Vd group (76.4% vs. 62.3%, p=0.0012). Patients who had received only one prior line of therapy also demonstrated a higher ORR on the SVd arm as compared to the Vd arm (80.8% vs. 65.7%, p=0.0082). 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, 16.9% of patients on the SVd arm achieved a Complete Response or a Stringent Complete Response as compared to 10.6% of patients receiving Vd therapy. All responses were confirmed by an IRC.

Data at the time of analysis showed a trend toward an overall survival (OS) benefit associated with SVd therapy with fewer deaths, numerically, reported on the SVd arm (47 vs. 62). Median OS for the SVd arm had not yet been reached as of the data cut-off date of February 18, 2020, while the median OS for the Vd arm was 25.0 months. The median OS for the SVd arm will be reported once it is reached and becomes available.

Peripheral neuropathy (PN) rates were significantly lower on SVd compared to Vd (32.3% vs. 47.1%; p=0.0010). In addition, PN rates of grade ≥2 were also significantly lower in the SVd arm compared to Vd (21.0% vs. 34.3%, P=0.0013).

The most common treatment-emergent adverse events (AEs) were cytopenias, along with gastrointestinal and constitutional symptoms and were consistent with those previously reported from other selinexor studies. Most AEs were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (50%), fatigue (42%), decreased appetite (35%), and

diarrhea (32%) and were mostly Grade 1 and 2 events. The most common Grade 3 and 4 treatment-related AEs were thrombocytopenia (39%), anemia (16%), and fatigue (13%).

**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 current indication to include the treatment for patients with multiple myeloma after at least one prior line of therapy has been accepted for filing by the FDA. 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 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 ($CL_{CR}$ <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. 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; 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 E.U. as a result of data from the STORM study or confirmatory approval in the U.S. or E.U. 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 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 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.

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For further information: Investors: Karyopharm Therapeutics Inc., Ian Karp, Senior Vice President, Investor and Public Relations, 857-297-2241 | ikarp@karyopharm.com, or Media: FTI Consulting, Simona Kormanikova or Robert Stanislaro, 212-850-5600 |Simona.Kormanikova@fticonsulting.com or robert.stanislaro@fticonsulting.com

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