Karyopharm Announces Dosing of First Patients in Two New Company-Sponsored Clinical Studies in Melanoma and Myelofibrosis

NEWTON, Mass., July 28, 2021 /PRNewswire/ -- Karyopharm Therapeutics Inc. (NASDAQ: KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, today announced dosing of the first patients in two new company-sponsored Phase 2 and 1/2 clinical studies evaluating XPOVIO® (selinexor), the Company's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound in combination with approved therapies in patients with advanced melanoma and in patients with treatment naïve myelofibrosis. These company-sponsored studies follow encouraging results from preclinical research and earlier stage, investigator-sponsored clinical studies conducted by Karyopharm's scientific collaborators.

"Despite recent advances in treatment options for both metastatic melanoma and myelofibrosis, far too many patients either do not respond or have short-lived responses to currently available treatment options, making the development of novel drug treatment approaches incredibly important for these diseases," said Sharon Shacham, PhD, MBA, Chief Scientific Officer of Karyopharm. "Substantial need remains for continued research into new druggable targets and identifying multiple targets and pathways that have the potential to be inhibited synergistically using combination approaches. We believe XPOVIO's oral administration, along with its novel mechanism of action, make it a promising treatment candidate for new, single and synergistic combination regimens across both hematologic and solid tumors."

Summary of Newly Initiated Clinical Studies:

A Phase 2 Study Evaluating XPOVIO in Combination with Keytruda® (pembrolizumab) in Recurrent Advanced Melanoma

This Phase 2, multicenter, open-label study (XPORT-MEL-033; NCT04768881) will evaluate the safety and efficacy of XPOVIO in combination with Keytruda® and is expected to enroll approximately 40 patients with locally advanced or metastatic melanoma that is resistant to initial checkpoint inhibitor therapy. Patients will receive once-weekly oral XPOVIO (80mg) and Keytruda® (400mg intravenously once every six weeks) until disease progression, toxicity or withdrawal from the study, whichever occurs first. The primary endpoint of the study is overall response rate (ORR). Secondary endpoints include safety, progression-free survival, overall survival (OS), and complete response rate, among several others.

Preclinical studies have shown that XPOVIO selectively kills malignant melanoma cells and synergistically increases the antitumor activity of check point inhibitors[1,2,3]. Two early clinical studies, one investigating XPOVIO as a single agent[4] and one investigating XPOVIO plus Keytruda[5], in heavily pretreated advanced melanoma, have shown that this activity is borne out in clinical studies.

A Phase 1/2 Study Evaluating XPOVIO in Combination with Jakafi® (ruxolitinib) in Treatment Naïve Myelofibrosis

This global Phase 1/2, multicenter, open-label study (XPORT-MF-034; NCT04562389) will evaluate the safety and efficacy of XPOVIO in combination with Jakafi® and is expected to enroll approximately 237 patients with treatment naïve myelofibrosis. The study will be conducted in two phases: Phase 1a/1b and

Phase 2. The Phase 1a dose escalation portion of the study will determine the maximum tolerated dose and the recommended Phase 2 dose (RP2D) and will evaluate safety and preliminary efficacy. The Phase 1b dose expansion portion of the study will be conducted at the determined RP2D and will further assess the safety and preliminary efficacy at this dose level. In the Phase 2 portion of the study, patients will be randomized 1:1 to receive either once weekly XPOVIO plus Jakafi® (15mg or 20mg twice daily) or Jakafi® (15mg or 20mg twice daily) monotherapy. The primary endpoint for the Phase 2 portion of the study is the percentage of patients who achieve spleen volume reduction of at least 35% from baseline. Secondary endpoints for the Phase 2 portion of the study include safety, percentage of patients who achieve total symptom score reduction of ≥50%, OS, anemia response and ORR, among several others.

This new Phase 1/2 study is supported by multiple preclinical data sets which showed that (i) nuclear cytoplasmic transport is essential for survival of $JAK2^{V617F}$-mutant HEL cells *in vitro*, a major vulnerability and a potential therapeutic target in MF[6], (ii) that XPOVIO significantly reduced white blood cells (WBCs), granulocytes and spleen GFP+ cells in *in vivo* models of $JAK2^{V617F}$-driven myeloproliferative neoplasms, and (iii) the combination of XPOVIO and ruxolitinib *in vivo* showed significant reduction in WBCs, granulocytes, spleen GFP+ cells, as well as in spleen weight when compared to either agent alone[7]. Collectively, these data support the clinical investigation of XPOVIO combined with ruxolitinib in patients with myelofibrosis.

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. NEXPOVIO® (selinexor) has also been granted conditional marketing authorization for adult patients with heavily pretreated multiple myeloma by the European Commission. 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 two 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) 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

XPOVIO® (selinexor) is a prescription medicine approved:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (XVd).
- In combination with dexamethasone 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 (Xd).
- 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 2 lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

SELECT IMPORTANT SAFETY INFORMATION
Warnings and Precautions

- Thrombocytopenia: Monitor platelet counts throughout treatment. Manage with dose interruption and/or reduction and supportive care.
- Neutropenia: Monitor neutrophil counts throughout treatment. Manage with dose interruption and/or reduction and granulocyte colony-stimulating factors.
- Gastrointestinal Toxicity: Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dose interruption and/or reduction, antiemetics, and supportive care.
- Hyponatremia: Monitor serum sodium levels throughout treatment. Correct for concurrent hyperglycemia and high serum paraprotein levels. Manage with dose interruption, reduction, or discontinuation, and supportive care.
- Serious Infection: Monitor for infection and treat promptly.
- Neurological Toxicity: Advise patients to refrain from driving and engaging in hazardous occupations or activities until neurological toxicity resolves. Optimize hydration status and concomitant medications to avoid dizziness or mental status changes.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential and males with a female partner of reproductive potential, of the potential risk to a fetus and use of effective contraception.
- Cataract: Cataracts may develop or progress. Treatment of cataracts usually requires surgical removal of the cataract.

Adverse Reactions

- The most common adverse reactions (≥20%) in patients with multiple myeloma who receive XVd are fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract and vomiting. Grade 3-4 laboratory abnormalities (≥10%) are thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia. In the BOSTON trial, fatal adverse reactions occurred in 6% of patients within 30 days of last treatment. Serious adverse reactions occurred in 52% of patients. Treatment discontinuation rate due to adverse reactions was 19%.
- The most common adverse reactions (≥20%) in patients with multiple myeloma who receive Xd are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea and upper respiratory tract infection. In the STORM trial, fatal adverse reactions occurred in 9% of patients. Serious adverse reactions occurred in 58% of patients. Treatment discontinuation rate due to adverse reactions was 27%.

- The most common adverse reactions (incidence ≥20%) in patients with DLBCL, excluding laboratory abnormalities, are fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3-4 laboratory abnormalities (≥15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. In the SADAL trial, fatal adverse reactions occurred in 3.7% of patients within 30 days, and 5% of patients within 60 days of last treatment; the most frequent fatal adverse reactions was infection (4.5% of patients). Serious adverse reactions occurred in 46% of patients; the most frequent serious adverse reaction was infection(21% of patients). Discontinuation due to adverse reactions occurred in 17% of patients.

Use In Specific Populations
Lactation: Advise not to breastfeed.

For additional product information, including full prescribing information, please visit **www.XPOVIO.com.**

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 first-in-class drugs directed against nuclear export for the treatment of cancer and other 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), is approved in the U.S. in multiple hematologic malignancy indications, including in combination with Velcade® (bortezomib) and dexamethasone for the treatment of adult patients with multiple myeloma after at least one prior therapy, in combination with dexamethasone for the treatment of adult patients with heavily pretreated multiple myeloma and as a monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma. NEXPOVIO® (selinexor) has also been granted conditional marketing authorization in combination with dexamethasone for adult patients with heavily pretreated multiple myeloma by the European Commission. 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 hematologic malignancies or certain solid tumors; 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 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 of its products or product candidates. 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, 2021, which was filed with the Securities and Exchange Commission (SEC) on May 4, 2021, 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.

References

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[4] Abdul Razak AR, et al. J Clin Oncol. 2016 Dec 1;34(34):4142.

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SOURCE Karyopharm Therapeutics Inc.

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