Karyopharm Announces Dosing of First Patient in a Phase 1/2 Study of Selinexor in Combination with Standard of Care Therapy for Patients with Newly Diagnosed or Recurrent Glioblastoma

NEWTON, Mass., June 09, 2020 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), an innovation-driven pharmaceutical company, today announced dosing of the first patient in a Phase 1/2 clinical study evaluating oral selinexor in combination with standard of care therapy in patients with newly diagnosed or recurrent glioblastoma (GBM). This global study is expected to enroll approximately 400 patients at clinical sites in the U.S., Europe, and Israel.

Selinexor is an oral selective inhibitor of nuclear export (SINE) compound which blocks the cellular protein XPO1, whose function includes playing a key role in regulating the activity of tumor suppressor proteins and other oncoproteins relevant in cancer cell biology. XPO1 may be an important, novel target in the treatment of patients with GBM as it is frequently overexpressed in both GBM and in high-grade gliomas, and the degree of XPO1 over-expression correlates with higher tumor grade and poor overall patient survival. Nonclinical studies indicate that selinexor has potent anti-GBM activity as monotherapy and is synergistic when combining with radiation, temozolomide and lomustine. Additionally, in previous clinical studies (KING study/NCT01986348), selinexor has demonstrated that it crosses the blood-brain barrier with adequate intra-tumoral penetration and single-agent efficacy with durable response and disease stabilization in heavily pretreated GBM patients further supporting the rationale for clinical development of selinexor to treat patients with brain cancers.

The randomized, multi-center, Phase 1/2 study (XPORT-GBM-029/NCT04421378) will be conducted in two phases: a Phase 1 dose finding study followed by a Phase 2 randomized efficacy exploration study, designed to independently evaluate three different combination regimens in three treatment arms in patients with newly diagnosed GBM (Arms A and B) or with recurrent GBM (Arm C). Arms A and B will investigate selinexor in combination with radiation therapy with or without the addition of temozolomide, while Arm C will evaluate the combination of selinexor and lomustine. The primary endpoints in the study are progression-free survival in patients with newly diagnosed GBM and overall survival (OS) in patients with recurrent GBM.

Yazmín Odia, M.D., Chief of Neuro-Oncology at Miami Cancer Institute, Baptist Health South Florida (BHSF), and investigator in the study, stated, “We are very excited about the launch of this innovative clinical trial on behalf of our patients who desperately need new treatment options for what is typically an incurable disease and given the few meaningful therapeutic advances in recent years.”

“We are hopeful that this study evaluating the activity of selinexor in combination with currently used standard treatments will help us further identify promising novel approaches for the treatment of patients with both newly diagnosed and recurrent GBM,” commented Minesh Mehta, M.D., Chief of Radiation Oncology at Miami Cancer Institute, BHSF, and investigator in the study.

“While selinexor has been most extensively studied in patients with hematologic malignancies, there is increasing evidence that selinexor may also play an important role in the treatment of a variety of solid tumors, including patients with GBM,” said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. “We were highly encouraged by the results from our previous Phase 2 KING study, which evaluated selinexor as a single agent in patients with recurrent GBM and demonstrated clear anti-cancer activity. We now look forward to assessing selinexor’s activity in combination with currently used standard of care treatments where we hope it will prove to be synergistic and even more effective.”

Selinexor, marketed as XPOVIO®, is currently approved by the U.S. Food and Drug Administration (FDA) as a treatment for patients with relapsed or refractory multiple myeloma. Selinexor is currently the only XPO1 inhibitor approved by the FDA and has been extensively tested in clinical trials across numerous cancer indications worldwide since 2012. Karyopharm has also submitted two additional supplemental New Drug Applications for XPOVIO which are currently under review by the FDA; one is for an expansion of XPOVIO’s label to include XPOVIO as a treatment for patients with multiple myeloma after at least one prior line of therapy and the other for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

About GBM

Glioblastoma Multiforme (GBM) is one of the most common and particularly aggressive forms of brain tumors of primarily glial cell origin. GBM is diagnosed in patients at a median age of 64 years but can occur at any age, including in childhood. GBM is an incurable disease and the prognosis for patients is typically poor due in part to its aggressive and extensive infiltration of surrounding central nervous system tissue and its frequent inaccessibility for surgical resection within the brain. In addition, the blood-brain barrier presents an obstacle for many chemotherapeutic agents, with only small, lipophilic molecules able to reach the tumor. Median survival in patients with newly diagnosed GBM is approximately 15 months and approximately five to seven months in patients with recurrent disease.

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. A supplemental New Drug Application was accepted by the FDA seeking accelerated approval for selinexor as a new treatment for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and selinexor has received Fast Track and Orphan designation and Priority Review from the FDA with a scheduled PDUFA date of June 23, 2020 for this patient population. Selinexor is also being evaluated in several other mid-and later-phase clinical trials across multiple cancer indications, including in multiple myeloma in a pivotal, randomized Phase 3 study in combination with Velcade® (bortezomib) and low-dose dexamethasone (BOSTON), for which Karyopharm announced positive top-line results in March 2020. In May 2020, Karyopharm submitted a supplemental New Drug Application based on data from the Phase 3 BOSTON study. Additional, ongoing trials for selinexor include 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:

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IMPORTANT SAFETY INFORMATION

Thrombocytopenia

XPOVIO can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with XPOVIO. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia and fatal hemorrhage occurred in <1% of patients.

Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two 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 and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia

XPOVIO can cause neutropenia, potentially increasing the risk of infection. Neutropenia was reported as an adverse reaction in 34% of patients, and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with XPOVIO. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity

Gastrointestinal toxicities occurred in patients treated with XPOVIO.

Nausea/Vomiting

Nausea was reported as an adverse reaction in 72% of patients, and Grade 3 nausea occurred in 9% of patients treated with XPOVIO. The median time to onset of the first nausea event was 3 days.

Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with XPOVIO. The median time to onset of the first vomiting event was 5 days.

Provide prophylactic 5-HT3 antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated.

Diarrhea

Diarrhea was reported as an adverse reaction in 44% of patients, and Grade 3 diarrhea occurred in 6% of patients treated with XPOVIO. The median time to onset of diarrhea was 15 days.

Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk.

Anorexia/Weight Loss

Anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with XPOVIO. The median time to onset of anorexia was 8 days.

Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

Hyponatremia

XPOVIO can cause hyponatremia; 39% of patients treated with XPOVIO experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days.

Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Infections

In patients receiving XPOVIO, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly reported Grade ≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms.

Neurological Toxicity

Neurological toxicities occurred in patients treated with XPOVIO.

Neurological adverse reactions including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients, and severe events (Grade 3-4) occurred in 9% of patients treated with XPOVIO. Median time to the first event was 15 days.

Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

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 (incidence ≥20%) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose,

and 65.3% had the dose of XPOVIO interrupted. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%.

Please see XPOVIO Full Prescribing Information available at www.XPOVIO.com.

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 May 2020, Karyopharm submitted a supplemental New Drug Application requesting approval for XPOVIO as a new treatment for patients with multiple myeloma after at least one prior line of therapy based on the data from the Phase 3 BOSTON study. A Marketing Authorization Application for selinexor is also currently under review by the European Medicines Agency. A supplemental New Drug Application was also accepted by the FDA seeking accelerated approval for selinexor as a new treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). 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 selinexor as a potential treatment for patients with GBM; the design and execution of a global randomized clinical trial to study this potential application of selinexor and the therapeutic potential of and potential clinical development plans for Karyopharm's drug candidates. 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 complete necessary clinical development phases of selinexor in this indication; that data from a clinical trial of selinexor would support its use in treatment of patients with GBM; or that regulators will approve the use of selinexor in patients with GBM. 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 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 selinexor for treatment of GBM in the commercial marketplace, the timing and costs involved in commercializing selinexor for such indication or any of Karyopharm's drug candidates that receive regulatory approval; the ability to retain regulatory approval of selinexor for such indication 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, 20, which was filed with theSecurities 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.

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