

Karyopharm Announces Publication of XPOVIO™ (Selinexor) Phase 2b STORM Study Results in The New England Journal of Medicine

-- XPOVIO was Recently Approved by the FDA for the Treatment of Patients with Multiple Myeloma whose Disease is Refractory to Proteasome Inhibitors, Immunomodulatory Agents, and an Anti-CD38 Monoclonal Antibody --
-- In STORM, XPOVIO Achieved a 26% Overall Response Rate, 8.6 Month Median Overall Survival and 15.6 Month Median Survival in the 39% of Patients with Minimal Response or Better --

NEWTON, Mass., Aug. 21, 2019 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), an oncology-focused pharmaceutical company, today announced that the results of the Phase 2b STORM study evaluating XPOVIO™ (selinexor) in patients with heavily pretreated, triple class refractory multiple myeloma were published [online](#) today in the New England Journal of Medicine. The STORM study evaluated XPOVIO, the Company's first-in-class, oral SINE compound, and low-dose dexamethasone in patients with triple class refractory multiple myeloma who were previously treated with all five of the most commonly prescribed anti-myeloma therapies currently available. XPOVIO received accelerated approval in the U.S. from the Food and Drug Administration (FDA) on July 3, 2019 for the treatment of adult patients with relapsed or 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. 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 a confirmatory trial.

Sundar Jagannath, MD, Tisch Cancer Institute at Mount Sinai School of Medicine, principal investigator of the STORM study and co-lead author of the manuscript, said, "The data from the STORM study demonstrate that oral selinexor, a first-in-class XPO1 inhibitor, combined with dexamethasone twice weekly, resulted in a response rate of 26% in heavily pretreated patients. The characteristics of the patients in the STORM study, including being heavily pretreated, yet still experiencing rapidly progressing disease, are consistent with the growing population of patients who have exhausted available myeloma therapies, but still desire to continue therapy. Of particular significance, for the 39% of patients who had a minimal response (MR) or better, overall survival (OS) was 15.6 months, compared to 1.7 months in patients whose disease progressed or where response was not evaluable."

"Despite the availability of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), alkylating agents and monoclonal antibodies for the treatment of multiple myeloma, most patients will, regrettably, have disease that continues to progress. An increasing number of patients are developing highly refractory disease and have no remaining treatment options of known clinical benefit," added Paul G. Richardson, MD, Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute, and co-lead author of the manuscript.

"We are pleased to have the STORM study results published in such a highly esteemed, peer-reviewed journal and this publication further supports the potential utility of oral XPOVIO in patients with highly refractory multiple myeloma," said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. "With the recent accelerated approval of oral XPOVIO, patients with heavily pretreated myeloma now have a new therapeutic option to treat their disease."

A Marketing Authorization Application (MAA) seeking conditional approval for selinexor is currently under review by the European Medicines Agency and Karyopharm expects to receive a decision on the MAA by the end of 2019 or early 2020.

The full Prescribing Information for XPOVIO is available at www.XPOVIO.com.

The Phase 2b STORM Study Results

The published results are from Part 2 of the international, multi-center, single-arm Phase 2b STORM (Selinexor Treatment of Refractory Myeloma) study (NCT02336815), which enrolled 122 patients with heavily pretreated, triple class refractory multiple myeloma in the U.S. and Europe. These heavily pretreated patients had a median of seven previous therapeutic regimens, including a median of 10 unique anti-myeloma agents. Specifically, the myeloma patients who were eligible for the study had prior exposure to the two PIs, Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two IMiDs, Revlimid® and Pomalyst, and the anti-CD38 monoclonal antibody Darzalex, as well as alkylating agents, and their disease was refractory to glucocorticoids, at least one PI, at least one IMiD, Darzalex, and their most recent therapy. Patients in the STORM study had rapidly progressing myeloma, with a 22% increase in disease burden in the 12 days from screening to initial therapy.

Given the rapid progression of penta-exposed, triple-class refractory myeloma, the window of opportunity to prevent further

illness and death is small. Therefore, the regimen that was used in the STORM study began with a high dose of selinexor to achieve rapid disease control. Each patient started 80mg oral selinexor twice weekly in combination with low-dose dexamethasone (dex; 20mg twice weekly). Because most patients involved in the study were older and frail, with limited end-organ reserve and at increased risk for adverse events, dose modifications were anticipated and were specified along with supportive care in the protocol.

For the STORM study's primary endpoint, oral selinexor achieved an overall response rate of 26% (95% confidence interval [CI], 19, 35), including two (2%) stringent complete responses (sCRs), six (5%) very good partial responses and 24 (20%) partial responses (PRs), and the trial therefore met its primary endpoint. Both patients who had relapsed after CAR-T therapy achieved PRs. Minimal response per IMWG criteria was observed in 16 (13%) patients and 48 patients (39%) had stable disease. Median time to partial response or better was 4.1 weeks. Clinical benefit rate (\geq minimal response), was 39% (95% CI, 31, 49). All responses were adjudicated by an Independent Review Committee.

Median duration of response was 4.4 months (95% CI, 3.7, 10.8). Progression-free survival was 3.7 months (95% CI, 3.0, 5.3) and OS was 8.6 months (95% CI, 6.2, 11.3). In the 39% of patients who achieved a partial or minimal response or better, median OS was 15.6 months, compared to a median OS of 1.7 months in patients whose disease progressed or where response was not evaluable ($p < 0.0001$).

The adverse events that were observed in the study were a function of dose, schedule, and baseline clinical characteristics (e.g., cytopenias). The most common treatment-emergent adverse events (AEs) were thrombocytopenia (73%), fatigue (73%), nausea (72%) and anemia (67%). The most common Grade 3/4 treatment-emergent AEs were thrombocytopenia (59%), anemia (44%), hyponatremia (22%) and neutropenia (21%). Importantly, most non-hematologic AEs were limited in severity to Grades 1 or 2, with only 10% experiencing Grade 3 nausea and 3% experiencing grade 3 vomiting. In all, 18% of patients discontinued study treatment because of an AE considered by the investigator related to study drug, though such determinations for a new agent are imprecise. AEs leading to dose modification or holds occurred in 80% of patients, with the majority occurring in the first 2 cycles. The most common AEs leading to dose reduction or interruption were thrombocytopenia (43%), fatigue (16%), and neutropenia (11%). Supportive care, including granulocyte colony stimulating factors, thrombopoietin receptor agonists, optimization of fluid and caloric intake, appetite stimulants, psychostimulants and/or additional anti-nausea agents usually reduced the intensity and/or duration of AEs. Side effects were reversible without evidence of toxic effects in major organs (treatment-related cardiac, pulmonary, hepatic, or renal dysfunction of grade 3 or higher) or cumulative toxic effects, with irreversible acute kidney injury reported in 1 patient (1%). Serious AEs occurred in 63% of patients, with pneumonia (11%), and sepsis (9%) being the most common. Twenty-eight patients died during the study: 16 from disease progression and 12 from an AE. Of these 12 patients, two were assessed by the investigator as related to treatment (pneumonia with concurrent disease progression [$n=1$], sepsis [$n=1$]).

The patient population described in this publication does not represent the population which formed the basis of XPOVIO's accelerated FDA approval. The approval of XPOVIO was based upon the efficacy and safety in a pre-specified sub-group analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pre-treated population than in the overall trial population. The overall response rate in this patient population was 25.3%.

About Multiple Myeloma

According to the National Cancer Institute (NCI), multiple myeloma is the second most common cancer of the blood in the U.S. with more than 32,000 new cases each year and over 130,000 patients living with the disease. 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 2019.

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. In addition to receiving accelerated 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. Selinexor is also being studied in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In 2018, Karyopharm reported positive top-line results from the Phase 2b SADAL study evaluating selinexor in patients with relapsed or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Selinexor has received Fast Track designation from the FDA for the patient population evaluated in the SADAL study. 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), as a potential backbone therapy in combination with approved therapies (STOMP), in liposarcoma (SEAL), in recurrent gliomas (KING) 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.

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 $\geq 20\%$) 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 oncology-focused 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 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 FDA in July 2019 in combination with dexamethasone as a treatment for patients with heavily pretreated multiple myeloma. A Marketing Authorization Application for selinexor is also currently under review by the European Medicines Agency (EMA). 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 our expectations relating to XPOVIO for the treatment of patients with RRMM, commercialization of XPOVIO or any of our drug candidates, submissions to, and the review and potential approval of selinexor by, regulatory authorities, including the anticipated timing of such submissions and actions and the potential availability of accelerated approval pathways, 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 regulators will agree that selinexor qualifies for conditional approval in the E.U. as a result of the data from the STORM study or accelerated or conditional approval in the U.S. or EU, respectively, based on data from the SADAL study in patients with relapsed or refractory DLBCL, 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 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 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; 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 diseases 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 June 30, 2019, which was filed with the Securities and Exchange Commission (SEC) on August 7, 2019, 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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