Karyopharm Announces Favorable Change in Co-Primary Endpoint for Pivotal Phase 3 SENTRY Trial in Myelofibrosis

Co-primary Endpoint Changed to Absolute Total Symptom Score (Abs-TSS) from Total Symptom Score Improvement of ≥ 50% (TSS50) Following Alignment with the FDA

Spleen Volume Response Rate ≥ 35% (SVR35) Remains a Co-primary Endpoint

Promising Improvement in Abs-TSS and SVR35 from Phase 1 Trial of Selinexor in Combination with Ruxolitinib Adds Confidence in Phase 3 SENTRY Trial

Proactively Increasing Total Sample Size of the SENTRY Trial to Approximately 350 Patients to Further Increase the Statistical Powering; Expected Top-line Data Read-out Remains in 2H 2025

Company to Host a Conference Call Today at8:00 a.m. ET Featuring Drs. Raajit Rampal and John Mascarenhas

NEWTON, Mass., Oct. 31, 2024 /PRNewswire/ -- Karyopharm Therapeutics Inc. (Nasdaq: KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, today announced that, following feedback from the U.S. Food and Drug Administration (FDA), the Company will be replacing TSS50, one of the co-primary endpoints in the Phase 3 SENTRY Trial (NCT04562389) with Abs-TSS. Abs-TSS measures the average improvement in patient symptom scores over 24 weeks relative to the patient's baseline symptom score.

"There remains a tremendous unmet need in myelofibrosis, as less than half of patients achieve SVR35 with each of the approved JAK inhibitors and many patients eventually stop responding to these treatments," said Dr. Raajit Rampal, Director of the Center for Hematologic Malignancies and Director of the Myeloproliferative Neoplasms Program at Memorial Sloan Kettering Cancer Center. "The Phase 1 trial, which evaluates the combination of selinexor and ruxolitinib, shows an approximate doubling of SVR35 to nearly 80% compared to historical JAKi monotherapy, and meaningful improvements in Abs-TSS with an average 18.5 point improvement at week 24 compared to baseline. I believe these data are meaningful and impressive and provide a strong rationale for the Phase 3 SENTRY trial."

Data from the Company's Phase 1 trial, evaluating the combination of selinexor 60mg plus ruxolitinib in JAKi naïve myelofibrosis patients, demonstrated that 79% of patients in the intent to treat population (n=14) achieved SVR35 and an average Abs-TSS improvement of 18.5 points in the efficacy evaluable population (n=9), at week 24 relative to baseline. Acknowledging the small sample size, these data are favorable to historical ruxolitinib monotherapy data which indicates that less than half of patients achieve SVR35 and an Abs-TSS improvement of 11 to 14 points[1]. The safety profile remains consistent and no new safety signals have been identified.

"Our confidence in the success of our Phase 3 SENTRY trial increases based on the change in the co-primary endpoint to Abs-TSS, the increased sample size and the data previously presented from our Phase 1 trial evaluating selinexor plus ruxolitinib in JAKi naïve myelofibrosis patients," said Reshma Rangwala, MD, PhD, Chief Medical Officer and Head of Research at Karyopharm. "Based upon strong enrollment, we remain on track to report top-line results in the second half of 2025."

"Improving symptomatic burden for patients with myelofibrosis is an important goal in therapy, directly linking to decreases in morbidity and likely mortality", said Dr. Ruben Mesa, President of Atrium Health Levine Cancer and Charles L. Spurr, MD Professor of Internal Medicine, Wake Forest University School of Medicine. "I am very encouraged by the benefits reported in Karyopharm's Phase 1 trial of selinexor combined with standard of care ruxolitinib, especially regarding disease associated symptoms. Additionally, I am grateful that the ongoing Phase 3 trial will use Abs-TSS as a co-primary endpoint, which may better represent the cumulative benefit patients experience on symptom burden."

Abs-TSS is an accepted measure that has been used in other Phase 3 clinical trials in myelofibrosis to evaluate the benefit/risk of an add-on treatment, such as selinexor, to the current standard of care. The change to Abs-TSS is strongly supported by key leading investigators and patient advocacy organizations, which generally view improvement in Abs-TSS from baseline as a more accurate assessment of symptom improvement in head-to-head clinical trials, such as SENTRY.

"We are vocal advocates for evolving myelofibrosis clinical trial endpoints. Growing data that support a newer outcome measure like Abs-TSS that is also meaningful to patients is very encouraging," said Kapila Viges, Chief Executive Officer, MPN Research Foundation. "Efforts to develop effective treatments and combination therapies with patients' goals for care in mind are important. For myelofibrosis patients and their families, options matter."

Company Conference Call Information

Karyopharm will host a conference call with management and Drs. Raajit Rampal and John Mascarenhas to discuss the Phase 3 SENTRY trial today, October 31, 2024, at 8:00 a.m. Eastern Time. To access the conference call, please dial (800) 836-8184 (local) or (646) 357-8785 (international) at least 10 minutes prior to the start time and ask to be joined into the Karyopharm Therapeutics call. A live audio webcast, along with accompanying slides, 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.

References

[1]Phase 3 MANIFEST trial. Rampal R, et al. ASH 2023. Oral 628; Phase 3 TRANSFORM-1 trial Pemmaraju N, et al. ASH 2023 abstract 620.

About the Phase 3 SENTRY Trial

SENTRY (NCT04562389) is a pivotal, Phase 3 clinical trial evaluating a once-weekly dose of 60mg of selinexor in combination with twice-daily ruxolitinib versus placebo plus ruxolitinib in JAKi naïve patients with platelet counts $\geq$100 x 10^9/L. Karyopharm intends to enroll approximately 350 JAKi naïve patients with myelofibrosis in this Phase 3 trial; patients are randomized 2-to-1 to the selinexor arm. The co-primary endpoints will be spleen volume response rate ≥ 35% (SVR35) at week 24 and the change in absolute total symptom score (Abs-TSS) over 24 weeks relative to baseline.

About XPOVIO® (selinexor)

XPOVIO is a first-in-class, oral exportin 1 (XPO1) inhibitor and the first of Karyopharm's Selective Inhibitor of Nuclear Export (SINE) compounds to be approved for the treatment of cancer. XPOVIO functions by selectively binding to and inhibiting the nuclear export protein XPO1. XPOVIO is approved in the U.S. and marketed by Karyopharm in multiple oncology indications, including: (i) in combination with Velcade® (bortezomib) and dexamethasone (XVd) in patients with multiple myeloma after at least one prior therapy; (ii) in combination with dexamethasone in patients with heavily pre-treated multiple myeloma; and (iii) in patients with diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. XPOVIO (also known as NEXPOVIO® in certain countries) has received regulatory approvals in various indications in a growing number of ex-U.S. territories and countries, including but not limited to the European Union, the United Kingdom, China, South Korea, Canada, Israel and Taiwan. XPOVIO and NEXPOVIO is marketed by Karyopharm's partners, Antengene, Menarini, Neopharm and FORUS in China, South Korea, Singapore, Australia, Hong Kong, Germany, Austria, Israel and Canada.

Please refer to the local Prescribing Information for full details.

Selinexor is also being investigated in several other mid- and late-stage clinical trials across multiple high unmet need cancer indications, including in endometrial cancer and myelofibrosis.

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

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 whose dedication to pioneering novel cancer therapies is fueled by a belief in the extraordinary strength and courage of patients with cancer. Since its founding, Karyopharm has been an industry leader in oral compounds that address nuclear export dysregulation, a fundamental mechanism of oncogenesis. Karyopharm's lead compound and first-in-class, oral exportin 1 (XPO1) inhibitor, XPOVIO® (selinexor), is approved in the U.S. and marketed by the Company in three oncology indications. It has also received regulatory approvals in various indications in a growing number of ex-U.S. territories and countries, including Europe and the United Kingdom (as NEXPOVIO®) and China. Karyopharm has a focused pipeline targeting indications in multiple high unmet need cancers, including in multiple myeloma, endometrial cancer, myelofibrosis, and diffuse large B-cell lymphoma (DLBCL). For more information about our people, science and pipeline, please visit www.karyopharm.com, and follow us on LinkedIn and on X at @Karyopharm.

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 the ability of selinexor to treat patients with myelofibrosis and expectations with respect to the clinical development plans and potential regulatory submissions of selinexor for the treatment of myelofibrosis. 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 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 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 obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that

receive regulatory approval; Karyopharm's results of clinical trials and preclinical trials, including subsequent analysis of existing data and new data received from ongoing and future trials; 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 trials; 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 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; the direct or indirect impact of the COVID-19 pandemic or any future pandemic on Karyopharm's business, results of operations and financial condition; 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 June 30, 2024, which was filed with the Securities and Exchange Commission (SEC) on August 6, 2024, 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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