July 9, 2014

Threshold Announces Initiation of Dosing With TH-302/Bortezomib (Velcade (R))/Dexamethasone ("TBorD") in Final Stage of Ongoing Phase 1/2 Trial of Patients With Relapsed/Refractory Multiple Myeloma

SOUTH SAN FRANCISCO, CA -- (Marketwired) -- 07/09/14 -- Threshold Pharmaceuticals, Inc. (NASDAQ: THLD) today announced that dosing has started in the final stage of an ongoing Phase 1/2 trial of its investigational hypoxia-activated prodrug, TH-302, in combination with the proteasome inhibitor bortezomib (Velcade®) and low-dose dexamethasone ("TBorD") in patients with relapsed/refractory multiple myeloma, a cancer of the bone marrow.

Initial results from the dose-escalation and dose-expansion stages of the trial evaluating TH-302 and low-dose dexamethasone without bortezomib were recently presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO). As reported at ASCO, patients were heavily-pretreated (median 6.5 prior systemic therapies), and objective responses were observed in 5/16 (31%) patients (three partial responses and two minimal responses) treated at the maximum-tolerated dose of TH-302 (340 mg/m^2).[1]

"Data seen thus far are encouraging using the combination of TH-302 and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma," said Irene Ghobrial, M.D., Medical Oncologist at Dana-Farber/Brigham and Women's Cancer Center and Principal Investigator of the Phase 1/2 trial. "I would like to acknowledge the Blood Cancer Research Partnership for their significant role in facilitating rapid accrual of patients to this study. We are excited to initiate this final stage in which patients will receive TH-302, bortezomib, and dexamethasone, particularly in light of preclinical research demonstrating synergistic cytotoxicity of TH-302 and bortezomib."

In the U.S. and Europe, there are an estimated 66,000 new cases of multiple myeloma per annum.[2,3] Current standards of care include alkylating agents, proteasome inhibitors, and immunomodulatory drugs (IMiDs). New treatment options for patients with advanced multiple myeloma who experience relapse of their disease or who become refractory to standard therapies remains an area of unmet medical need.

"The presence of hypoxia in the diseased bone marrow may present a new therapeutic target for treating multiple myeloma and underscores my enthusiasm for further evaluation of TH-302 in this disease," said Jacob Laubach, M.D., Clinical Director of the Jerome Lipper Multiple Myeloma Center at Dana-Farber/Brigham and Women's Cancer Center and a lead investigator on the Phase 1/2 trial.

The bone marrow in patients with multiple myeloma has been shown to be hypoxic,[4,5] and hypoxia has been implicated in the progression of multiple myeloma *in vitro* and *in vivo*.[6] TH-302 is a hypoxia-activated prodrug that is designed to selectively release bromo-isophosphoramide mustard (Br-IPM), a potent DNA-alkylating agent, under conditions of tumor hypoxia. TH-302 has demonstrated antimyeloma activity both *in vitro* and *in vivo* as well as synergistic cytotoxic activity with bortezomib *in vitro*.[7-9]

About the Phase 1/2 Trial

The objectives of the ongoing Phase 1/2 trial combining TH-302 and dexamethasone with or without bortezomib include assessment of safety and tolerability, determination of dose-limiting toxicities and the maximum-tolerated dose of TH-302, and assessment of preliminary efficacy in patients with relapsed/refractory multiple myeloma.

The ASCO 2014 presentation included preliminary data from 24 patients in the dose-escalation and dose-expansion portions of the study who initiated treatment with TH-302 and low-dose dexamethasone prior to March 1, 2014; analyses reflected the clinical database as of May 19, 2014. Of these 24 patients, 17 were treated at the maximum tolerated dose of TH-302 (340 mg/m^2).

In these patients, the most common adverse events related to TH-302 were nausea and fatigue that occurred in at least 25% of the patients. The most common Grade 3/4 hematologic adverse events related to TH-302 were thrombocytopenia (29%) and leukopenia (25%). Dose-limiting toxicities of Grade 3 stomatitis were reported during the first treatment cycle for the first two patients treated at 480 mg/m^2 TH-302; therefore, the maximum tolerated dose of TH-302 in combination with low-dose dexamethasone was established at 340 mg/m^2, as previously reported.[10]

Of the 24 patients included in the ASCO presentation, 23 were evaluable for response. Best responses included four partial responses (4 PR), two minimal responses (2 MR), and 15 stable disease (15 SD) assessments; two patients had progressive disease (2 PD).

The clinical benefit rate for patients treated at the maximum tolerated dose of TH-302 (340 mg/m^2, n=16 evaluable patients) was 31% (comprised of 3 PR and 2 MR).

In the final stage of the trial to evaluate ***T***H-302, ***bor***tezomib, and low-dose ***d***examethasone ("TBorD"), an initial dose of TH-302 of 240 mg/m^2 will be administered twice weekly for the first two weeks of a three-week treatment cycle. The dose of TH-302 will be escalated in cohorts of 3-6 patients. The dose of bortezomib will remain fixed at 1.3 mg/m^2.

About TH-302

TH-302 is an investigational hypoxia-activated prodrug that is designed to be activated under tumor hypoxic conditions, a hallmark of many cancers. Areas of low oxygen levels (hypoxia) in solid tumors are due to insufficient blood supply as a result of aberrant vasculature. Similarly, the bone marrow of patients with hematological malignancies has also been shown, in some cases, to be severely hypoxic.

TH-302 is currently under evaluation in two Phase 3 trials: one in combination with doxorubicin versus doxorubicin alone in patients with soft tissue sarcoma, and the other in combination with gemcitabine versus gemcitabine and placebo in patients with advanced pancreatic cancer (the "MAESTRO" trial). Both Phase 3 trials are being conducted under Special Protocol Agreements with the U.S. Food and Drug Administration (FDA). The FDA and the European Commission have granted TH-302 Orphan Drug Designation for the treatment of soft tissue sarcoma and pancreatic cancer. TH-302 is also being investigated in earlier-stage clinical trials of other solid tumors and hematological malignancies, in combination with chemotherapy and antiangiogenic therapy, and for certain cancers, is being investigated as a monotherapy.

Threshold has a global license and co-development agreement for TH-302 with Merck KGaA, Darmstadt, Germany, which includes an option for Threshold to co-commercialize in the U.S.

About the Blood Cancer Research Partnership

The Leukemia & Lymphoma Society and Dana-Farber Cancer Institute have established a network of sites for clinical trial testing of innovative blood cancer therapies in community oncology settings across the country. This groundbreaking Blood Cancer Research Partnership (BCRP) brings clinical trials closer to where patients live and helps to address one of the primary bottlenecks in the development of new cancer therapies: the need for more patients to take part in trials.

About Threshold Pharmaceuticals

Threshold Pharmaceuticals, Inc. is a biotechnology company focused on the discovery and development of drugs targeting tumor hypoxia, the low oxygen condition found in microenvironments of most solid tumors as well as the bone marrows of some hematologic malignancies. This approach offers broad potential to treat a variety of cancers. By selectively targeting tumor cells, we are building a pipeline of drugs that hold promise to be more effective and less toxic to healthy tissues than conventional anticancer drugs. For additional information, please visit our website (www.thresholdpharm.com).

Forward-Looking Statements

Except for statements of historical fact, the statements in this press release are forward-looking statements, including statements regarding the potential therapeutic uses and benefits of TH-302, including TH-302's potential to be a component of new combination approaches to treating multiple myeloma. Potential risks and uncertainties include, but are not limited to: the ability of Threshold and Merck KGaA, Darmstadt, Germany, to enroll or complete TH-302 clinical trials; the time and expense required to conduct such clinical trials and analyze data; issues arising in the regulatory or manufacturing process and the results of such clinical trials (including product safety issues and efficacy results); the risk that preclinical studies in animal models of disease may not accurately predict the results of human clinical trials of TH-302; the risk that the final data from ongoing trials may be materially different from the preliminary data that Threshold has reported; Threshold's and Merck KGaA's (Darmstadt, Germany) dependence on single source suppliers, including the risk that these single source suppliers may be unable to meet clinical supply demands for TH-302 which could significantly delay the development of TH-302; risks related to Threshold's dependence on its collaborative relationship with Merck KGaA, Darmstadt, Germany, including its dependence on decisions by Merck KGaA, Darmstadt, Germany regarding the amount and timing of resource expenditures for the development of TH-302; and Threshold's need for and the availability of resources to develop TH-302 and to support Threshold's operations. Further information regarding these and other risks is included under the heading "Risk Factors" in Threshold's Quarterly Report on Form 10-Q, which has been filed with the Securities and Exchange Commission on May 1, 2014 and is available from the SEC's website (www.sec.gov) and on our website (www.thresholdpharm.com) under the heading "Investors." We undertake no duty to update any forward-looking statement made in this news release.

References

1. Laubach J, et al. Preliminary safety and efficacy of TH-302, an investigational hypoxia-targeted drug, and dexamethasone (dex) in patients (pts) with relapsed/refractory multiple myeloma (RR MM). *Journal of Clinical Oncology* 32: 8534, 2014.
2. American Cancer Society. Cancer Facts and Figures 2014.
http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf (accessed July 3, 2014).
3. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/online.aspx (accessed July 3, 2014).
4. Colla S, et al. Low bone marrow oxygen tension and hypoxia-inducible factor-1α overexpression characterize patients with multiple myeloma: role on the transcriptional and proangiogenic profiles of CD138(+) cells. *Leukemia* 24: 1967-1970, 2010.
5. Martin SK, et al. Hypoxia-inducible factor-2 is a novel regulator of aberrant CXCL12 expression in multiple myeloma plasma cells. *Haematologica* 95: 776-784, 2010.
6. Azab AK, et al. Hypoxia promotes dissemination of multiple myeloma through acquisition of epithelial to mesenchymal transition-like features. *Blood* 119: 5782-5794, 2012.

7. Hu J, et al. Targeting the multiple myeloma hypoxic niche with TH-302, a hypoxia-activated prodrug. *Blood* 116: 1524-1527, 2010.
8. Chesi M, et al. Drug response in a genetically engineered mouse model of multiple myeloma is predictive of clinical efficacy. *Blood* 120: 376-385, 2012.
9. Hu J, et al. Synergistic induction of apoptosis in multiple myeloma cells by bortezomib and hypoxia-activated prodrug TH-302, *in vivo* and *in vitro*. *Mol Cancer Ther* 12: 1763-1773, 2013.
10. Ghobrial IM, et al. Phase 1 study of TH-302, an investigational hypoxia-targeted drug, and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood* 122: 1948, 2013.

Contact

Laura Hansen, Ph.D.
Senior Director, Corporate Communications
Phone: 650-703-6523
E-mail: lhansen@thresholdpharm.com

Source: Threshold Pharmaceuticals

News Provided by Acquire Media