Onconova Announces Presentation of Mechanism of Action Studies of Rigosertib Combination with Azacitidine at American Association for Cancer Research (AACR) Epigenetics Conference

March 4, 2018

- Effect of rigosertib plus azacitidine treatment on epigenetic modulation in cancer cell-lines and patient derived bone marrow cells
- Study suggests potential novel clinical strategies to improve outcomes for patients with higher-risk Myelodysplastic Syndromes and reversal of resistance to treatment with epigenetic therapies

NEWTOWN, Pa., March 04, 2018 (GLOBE NEWSWIRE) -- Onconova Therapeutics, Inc. (NASDAQ:ONTX), a Phase 3 clinical-stage biopharmaceutical company focused on discovering and developing novel products to treat cancer, with a primary focus on Myelodysplastic Syndromes (MDS), announced the presentation of new data highlighting the mechanism of action of rigosertib in combination with azacitidine at the American Association for Cancer Research Special Conference on "Targeting DNA Methylation and Chromatin for Cancer Therapy."

Dr. Lewis Silverman of the Mount Sinai School of Medicine presented a study titled "Rigosertib Alone or in Combination with Azacitidine or Vorinostat has Chromatin Modifying Effects and Epigenetically Reprograms Hematopoietic Stem and Progenitor Cells in the Myelodysplastic Syndrome". The report is related to an ongoing clinical trial of rigosertib in combination with azacitidine. Initial results of this ongoing Phase 1/2 study in patients with MDS demonstrated a response rate of 76% overall, 62% in patients following hypomethylating agent (HMA) failure, and 85% in HMA naïve patients (Navada *et al*, EHA, 2017). The current report describes results of laboratory studies that compared molecular changes induced by single agent rigosertib and the combination of either azacitidine or vorinostat, two FDA approved therapies directed at epigenetic targets.

The epigenetic events modulated by rigosertib in combination with either agent resulted in global histone post-translational modifications, differential Pol II association with active histone marks, epigenetic reprogramming of pluripotency genes, and expansion of primitive hematopoietic pluripotent stem cells (HPSCs). As expected from the mechanism of action of rigosertib, the treated cells exhibited downregulation of the PI3K/AKT pathway and cell cycle checkpoint proteins. Importantly, the effects of rigosertib lead to HPSC reprogramming. Comparative assessment of changes induced by single agent and various combinations suggests that a specific pattern of epigenetic changes may be involved in the reversal of clinical epigenetic resistance to single agent treatment with hypomethylating agents and may contribute to enhanced hematopoietic function and response in the clinical setting. These nonclinical models also suggest potential novel clinical strategies to improve outcomes for patients with higher-risk MDS.

Dr. Lewis Silverman, the lead investigator of this laboratory study, commented, "These results add to a growing body of evidence that a combination regimen of oral rigosertib with azacitidine can improve outcomes for patients with higher-risk MDS, where the currently available therapies have a limited duration of benefit. Our studies reported here present the mechanistic context for the encouraging results from Onconova's Phase 2 trials, which are forming the basis of the Phase 3 trial design. By employing patient derived bone marrow stem cells from patients treated in clinical trials, we are planning to narrow down markers for evaluating the effect of treatment in future studies."

A copy of the presentation is available by visiting the Scientific Presentations section of Onconova's website.

About Onconova Therapeutics, Inc.

Onconova Therapeutics, Inc. is a Phase 3-stage biopharmaceutical company focused on discovering and developing novel small molecule drug candidates to treat cancer, with a primary focus on Myelodysplastic Syndromes (MDS). Rigosertib, Onconova's lead candidate, is a proprietary Phase 3 small molecule agent, which the Company believes blocks cellular signaling by targeting RAS effector pathways. Using a proprietary chemistry platform, Onconova has created a pipeline of targeted agents designed to work against specific cellular pathways that are important in cancer cells. Onconova has three product candidates in the clinical stage and several pre-clinical programs. Advanced clinical trials with the Company's lead compound, rigosertib, are aimed at what the Company believes are unmet medical needs of patients with MDS. For more information, please visit http://www.onconova.com.

About IV Rigosertib

The intravenous form of rigosertib has been employed in Phase 1, 2, and 3 clinical trials involving more than 800 patients, and is currently being evaluated in a randomized Phase 3 international INSPIRE trial for patients with higher-risk MDS, after failure of hypomethylating agent, or HMA, therapy.

About INSPIRE

The **IN**ternational **S**tudy of **P**hase III **I**V **R**igos**E**rtib, or INSPIRE, was finalized following guidance received from the U.S. Food and Drug Administration and European Medicines Agency and derives from the findings of the ONTIME Phase 3 trial. INSPIRE is a multi-center, randomized controlled study to assess the efficacy and safety of IV rigosertib in HR-MDS patients who had progressed on, failed to respond to, or relapsed after previous treatment with an HMA within the first 9 months or nine cycles over the course of one year after initiation of HMA treatment. This time frame optimizes the opportunity to respond to treatment with an HMA prior to declaring treatment failure, as per NCCN Guidelines. Following interim analysis in early 2018, the independent Data Monitoring Committee recommended that the trial continue with an expansion in enrollment to 360 patients based on a pre-planned sample size re-estimation. Patients are randomized at a 2:1 ratio into two treatment arms: IV rigosertib plus Best Supportive Care versus

Physician's Choice plus Best Supportive Care. The primary endpoint of INSPIRE is overall survival. Full details of the INSPIRE trial, such as inclusion and exclusion criteria, as well as secondary endpoints, can be found on clinicaltrials.gov (NCT02562443).

About Oral Rigosertib

The oral form of rigosertib was developed to provide more convenient dosing for use where the duration of treatment may extend to multiple years. This dosage form may also support many combination therapy modalities. To date, 368 patients have been treated with the oral formulation of rigosertib. Initial studies with single-agent oral rigosertib were conducted in hematological malignancies, lower-risk MDS, and solid tumors. Combination therapy of oral rigosertib with azacitidine and chemoradiotherapy has also been explored. Currently, oral rigosertib is being developed as a combination therapy together with azacitidine for patients with higher-risk MDS who require HMA therapy. A Phase 1/2 trial of the combination therapy has been fully enrolled and the preliminary results were presented in 2016. This novel combination is the subject of an issued US patent with earliest expiration in 2028.

Forward Looking Statements

Some of the statements in this release are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995, and involve risks and uncertainties. These statements relate to Onconova Therapeutics, Inc.'s expectations regarding the INSPIRE Trial. Although Onconova believes that the expectations reflected in such forward-looking statements are reasonable as of the date made, expectations may prove to have been materially different from the results expressed or implied by such forward-looking statements. Onconova has attempted to identify forward-looking statements by terminology including "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or other words that convey uncertainty of future events or outcomes. These statements are only predictions and involve known and unknown risks, uncertainties, and other factors, including Onconova's ability to continue as a going concern, the need for additional financing and current plans and future needs to scale back operations if adequate financing is not obtained, the success and timing of Onconova's clinical trials and regulatory approval of protocols, and those discussed under the heading "Risk Factors" in Onconova's most recent Annual Report on Form 10-K and quarterly reports on Form 10-Q.

Any forward-looking statements contained in this release speak only as of its date. Onconova undertakes no obligation to update any forward-looking statements contained in this release to reflect events or circumstances occurring after its date or to reflect the occurrence of unanticipated events.

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