Cyclacel Announces Dosing of First Patient in Phase 1/2 Study of Oral Fadraciclib in Patients With Leukemias or Myelodysplastic Syndromes

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Next-Generation CDK2/9 Inhibitor Fadraciclib to Be Evaluated as a Single Agent and in Combinations in Streamlined, Registration-Directed Study

BERKELEY HEIGHTS, N.J., Nov. 05, 2021 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (NASDAQ: CYCC, NASDAQ: CYCCP; "Cyclacel" or the "Company"), a biopharmaceutical company developing innovative medicines based on cancer cell biology, announced dosing of the first patient in the Company's multi-cohort Phase 1/2 study of oral fadraciclib in patients with leukemias or myelodysplastic syndromes (MDS).

"We are proud to have achieved this second key clinical milestone and corporate objective following the start of the oral fadraciclib Phase 1/2 solid tumor and lymphoma study last quarter," said Spiro Rombotis, Cyclacel's President and Chief Executive Officer. "After opening these two streamlined, registration-directed Phase 1/2 studies with fadraciclib as planned, we will next evaluate the clinical potential of oral CYC140, our PLK1 inhibitor, first in solid tumors and lymphomas and then in leukemias. We look forward to providing periodic updates on our clinical progress and data from these open-label studies when available."

"We are pleased to have dosed the first patient in this leukemia study and are delighted by the enthusiasm and strong interest from current and prospective investigators," said Mark Kirschbaum M.D., Senior Vice President and Chief Medical Officer of Cyclacel. "The study has initially opened at City of Hope, a world-renowned cancer research and treatment organization, with more sites to join later. We are building a distinguished, global network of participating institutions for this leukemia study, the ongoing solid tumor clinical study and also for preclinical collaborations. We are excited to begin this second mid-stage study of fadraciclib with the objective of registration-enabling outcomes as a single agent and in relevant combinations, potentially offering a new treatment option for patients with leukemias, MDS and related disorders."

"Based upon the mechanism of action and prior clinical activity shown to date, further exploration of this novel CDK2/9 inhibitor, both as a single-agent and in combinations, is warranted across a number of leukemias and MDS," said Brian Ball, M.D., Assistant Professor, Department of Hematology and Hematopoietic Cell Transplantation at City of Hope. "We look forward to enrolling patients in this trial, performing correlative studies, and evaluating potential treatment benefit for this experimental therapy, particularly in novel subsets of AML, which we have recently described and which may respond to inhibition of these targets."

The Phase 1/2 registration-directed trial, designated CYC065-102, uses a streamlined design and will first determine the recommended Phase 2 dose (RP2D) for single-agent, oral fadraciclib. Once RP2D has been established, the trial will immediately enter into proof-of-concept, cohort stage, using a Simon 2-stage design, where fadraciclib, both as a single agent and in combinations, will be administered to patients in up to seven cohorts relevant to the drug's mechanism of action and informed by the clinical activity of fadraciclib in previous studies.

Single-agent cohorts will include patients with acute myeloid leukemia (AML) or MDS who have an inadequate response or have progressed on venetoclax combinations with hypomethylating agent (HMA) or low dose Ara C; relapsed/refractory AML or MDS patients with FLT3, KIT or MAPK pathways (including N and K RAS, BRAF, PTPN11, NF1). The trial will also include patients with chronic lymphocytic leukemia (CLL) who have progressed after at least two lines of therapy including a BTK inhibitor and venetoclax.

Combination cohorts for patients with AML or MDS are: fadraciclib and azacitidine for patients with AML or MDS who progressed with hypomethylating (HMA) treatments and also fadraciclib and venetoclax for patients that have progressed after venetoclax therapy. A further combination cohort of fadraciclib and venetoclax will enroll patients with CLL or small lymphocytic lymphoma (SLL) who have progressed after venetoclax therapy. An additional basket cohort will evaluate patients with biomarkers relevant to the drug's mechanism, including MCL1 and MYC.

The protocol allows for expansion of a cohort based on response which may allow acceleration of the clinical development and registration plan for fadraciclib.

About Cyclin-Dependent Kinases and Fadraciclib

Cyclin-dependent kinases (CDKs) are critical for cell cycle control and transcriptional regulation. Dysregulated CDKs have been linked to the cancer hallmarks of uncontrolled proliferation and increased cancer cell survival. Fadraciclib, a next generation CDK inhibitor, is a highly selective, potent, orally and intravenously available, inhibitor of CDK2 and CDK9. CDK2 drives cell cycle transitions and CDK9 regulates transcription of genes through phosphorylation of the carboxy-terminal domain (CTD) of RNA polymerase II (RNAP II). By inhibiting CDK2 and CDK9 fadraciclib causes apoptotic death of cancer cells at sub-micromolar concentrations. Published data support the hypothesis that concomitant inhibition of CDK2 and CDK9 yields synergistic anti-tumor activity rather than inhibition of CDK2 or CDK9 alone.

Preclinical and animal model data suggest that fadraciclib may benefit patients with adult and pediatric hematological malignancies, such as ALL, AML, B-cell lymphoma, CLL, and multiple myeloma and certain cyclin E-addicted or MYC-amplified solid tumors, including certain forms of breast cancer, neuroblastoma, ovarian cancer and uterine serous carcinoma. Similarly to FDA-approved CDK4/6 inhibitors, fadraciclib may be useful in combination with other anticancer drugs, including HER2 inhibitors, such as trastuzumab, or BCL2 inhibitors, such as venetoclax.

Venetoclax has modest single-agent activity in AML. MCL1 dependence appears to correlate with resistance to venetoclax. A pre-clinical study confirmed synergy of fadraciclib and venetoclax, suggesting that the suppression of both BCL2 and MCL1 may be more beneficial than inhibiting

either protein alone.

Pre-existing or emergent mutations in the MAPK pathway contribute towards resistance to venetoclax, FLT3 inhibitors and mutant IDH inhibitors. These mutations are also frequent in proliferative CMML progressing to AML. Activating mutations in the MAPK pathway upregulates MCL1 and renders AML resistant to apoptosis. CDK9 inhibition downregulates MCL1 transcriptionally and can potentially be effective in the context of MAPK and other receptor tyrosine kinase mutations.

In a prior Phase 1 open-label trial (CYC065-01), patients with high copy CCNE (cyclin E), MYC or MCL1 showed sensitivity to intravenously-administered, single-agent fadraciclib. A heavily pretreated patient with MCL1 amplified endometrial cancer achieved a radiographically confirmed partial response (PR) after a month and a half on fadraciclib. This patient continues on therapy for almost two years and reduction in her target tumor lesions has reached 100%. An additional patient with cyclin E amplified ovarian cancer achieved stable disease with 29% shrinkage in her target tumor lesions.

References: Do, KT, et al., 32nd EORTC/AACR/NCI Virtual Symposium 24-25 Oct. 2020; Frame S et al, PLOS One, 2020; Frame et al, AACR, 2010, Abs 3886; Poon E et al, JCI 2020; Scaltriti M et al, PNAS, 2011.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel is a clinical-stage, biopharmaceutical company developing innovative cancer medicines based on cell cycle, transcriptional regulation and mitosis biology. The transcriptional regulation program is evaluating fadraciclib, a CDK2/9 inhibitor, and the anti-mitotic program CYC140, a PLK1 inhibitor, in patients with both solid tumors and hematological malignancies. Cyclacel's strategy is to build a diversified biopharmaceutical business based on a pipeline of novel drug candidates addressing oncology and hematology indications. For additional information, please visit www.cyclacel.com.

Forward-looking Statements

This news release contains certain forward-looking statements that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the efficacy, safety and intended utilization of Cyclacel's product candidates, the conduct and results of future clinical trials, plans regarding regulatory filings, future research and clinical trials and plans regarding partnering activities. Factors that may cause actual results to differ materially include the risk that product candidates that appeared promising in early research and clinical trials do not demonstrate safety and/or efficacy in larger-scale or later clinical trials, trials may have difficulty enrolling, Cyclacel may not obtain approval to market its product candidates, the risks associated with reliance on outside financing to meet capital requirements, the potential effects of the COVID-19 pandemic, and the risks associated with reliance on collaborative partners for further clinical trials, development and commercialization of product candidates. You are urged to consider statements that include the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "anticipates," "intends," "continues," "forecast," "designed," "goal," or the negative of those words or other comparable words to be uncertain and forward-looking. For a further list and description of the risks and uncertainties the Company faces, please refer to our most recent Annual Report on Form 10-K and other periodic and other filings we file with the Securities and Exchange Commission and are available at www.sec.gov. Such forward-looking statements are current only as of the date they are made, and we assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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