Cyclacel's Clinical Stage CDK2/9 Inhibitor Fadraciclib Targets Key Anti-Apoptotic and Oncogenic Pathways in Cancer

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-- Characterization of fadraciclib published in peer-reviewed journal shows specificity against

CDK2 and CDK9 and enablement of apoptosis of cancer cells driven by MCL1, cyclin E and/or MYC –

-- Data builds on growing body of evidence indicating the promise of dual CDK2/9 inhibition --

BERKELEY HEIGHTS, N.J. and DUNDEE, United Kingdom, July 13, 2020 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (Nasdaq: CYCC) (Nasdaq: CYCCP) (Cyclacel or the Company), a biopharmaceutical company developing innovative medicines based on cancer cell biology, today announced publication of a peer-reviewed study of fadraciclib, in *PLOS ONE*. The publication, authored by scientists from Cyclacel and The Institute of Cancer Research, London, describes the discovery of fadraciclib and shows its ability to target CDK2 and CDK9, leading to broad therapeutic potential.

"The published findings strengthen the mechanistic rationale for fadraciclib's potential as an anti-cancer therapy. Building upon previous research in CDK pathways, including the roles of cyclin E, MCL1 and MYC overexpression, the paper highlights the benefits of inhibiting both CDK2 and CDK9, two complementary cancer pathways," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "Independent findings reported at the ASCO20 Virtual Scientific Program corroborate the attractiveness of this dual targeting approach. Based on recently disclosed clinical data fadraciclib is establishing a leadership position among apoptosis enabling compounds in clinical development. We are encouraged by observations of single agent anticancer activity in our clinical studies. Initial clinical data with oral fadraciclib show concordance with intravenous pharmacokinetics. In parallel with evaluating fadraciclib in patients with acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS), we are executing a precision medicine strategy to evaluate fadraciclib in patients with solid tumors, with study enrollment expected to begin by Q1 2021."

"These exciting new findings revealing fadraciclib's chemical structure and describing its relevant anti-cancer properties, reflect the highly productive collaboration of ICR with Cyclacel to discover and develop innovative cancer treatments," said Professor Paul Workman, FMedSci, FRS, study co-author and Chief Executive and President, The Institute of Cancer Research, London, UK. "As a potent and selective inhibitor of CDK2 and CDK9, we believe our cumulative findings to-date support fadraciclib's ability to address key cancer pathways in solid tumors and leukaemias, indicating its potential as a new targeted anti-cancer therapy."

Cyclin-dependent kinases (CDKs) exist in many isoforms and as key cell cycle regulators can play a critical role in cancer growth. This preclinical characterization of fadraciclib includes its potency and selectivity against CDK2 and CDK9 *in vitro* and in a broad range of cancer cell lines including AML, breast and colorectal. Further *in vivo* efficacy was demonstrated in leukemia xenograft models.

Experimental results support fadraciclib's anti-cancer activity through CDK2/9 inhibition. In breast cancer cell lines, short-pulse treatment with fadraciclib showed preferential activity against transformed cells over normal cells. This finding supports the compound's potential benefit in cancers addicted to cyclin E which can be rationally targeted by CDK2 inhibition. In AML models, fadraciclib was effective in inhibiting CDK9 and suppressing the MCL1 protein to induce apoptosis or programmed cell death of leukemia cells. Fadraciclib also demonstrated synergy with BCL2 inhibitors such as venetoclax in AML cells. In subcutaneous mouse xenograft models of AML and MLLr-AML, nearly 100% tumor growth inhibition was achieved with oral administration of fadraciclib at pharmacological doses.

Publication Details

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About Cyclin-Dependent Kinases and Fadraciclib

Cyclin-dependent kinases (CDKs) are critical for cell cycle regulation and transcriptional elongation. Dysregulated CDKs have been linked to the cancer hallmarks of uncontrolled proliferation and increased survival. Fadraciclib (CYC065) is a potent orally and intravenously available inhibitor of CDK2 and CDK9. CDK9 regulates transcription of genes through phosphorylation of RNA polymerase II (RNAP II) C-terminal domain (CTD). Inhibition of CDK9 by fadraciclib suppresses CDK9-dependent gene expression and reduces the level of MCL1, a key anti-apoptotic protein.

Fadraciclib is in an ongoing Phase 1, first-in-human study in patients with advanced solid tumors. In this all-comer study, target engagement and durable suppression of the MCL1 biomarker were observed after a single dose of fadraciclib. Tumor shrinkage and stable disease were observed in five patients with cyclin E, MCL1 or MYC amplified advanced cancers. In the ongoing part 2 of the study evaluating a more intensive dosing regimen, a durable partial response has been observed in a heavily pretreated patient with MCL1-amplified endometrial cancer. Fadraciclib is also being evaluated in Phase 1 combination studies with venetoclax in relapsed or refractory CLL and in relapsed or refractory AML or MDS. Preclinical data suggest that fadraciclib may benefit patients with adult and pediatric hematological malignancies such as CLL, AML, ALL, B-cell lymphomas, 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.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel Pharmaceuticals is a clinical-stage biopharmaceutical company developing innovative cancer medicines based on cell cycle, transcriptional regulation and DNA damage response biology. The transcriptional regulation program is evaluating fadraciclib as a single agent in solid tumors and in combination with venetoclax in patients with relapsed or refractory AML/MDS and CLL. The DNA damage response program is evaluating an oral combination of sapacitabine and venetoclax in patients with relapsed or refractory AML/MDS. An investigator-sponsored trial (IST) is evaluating an oral combination of sapacitabine and olaparib in patients with BRCA mutant breast cancer. The anti-mitotic program is evaluating CYC140, a PLK1 inhibitor, in advanced leukemias/MDS patients. Cyclacel's strategy is to build a diversified biopharmaceutical business focused in hematology and oncology based on a pipeline of novel drug candidates. 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, 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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