Cyclacel Pharmaceuticals Announces Publication Confirming Fadraciclib Suppresses MCL1 and Synergizes With Venetoclax in Chronic Lymphocytic Leukemia

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-New Preclinical Data Highlight Fadraciclib's Apoptosis Enabling Mechanism in Leukemia-

-Remarkable Synergy Observed with Venetoclax, esp. in Resistant CLL cells with 17p Deletion-

BERKELEY HEIGHTS, N.J., April 12, 2022 (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 a publication in the journal *Leukemia* titled "**Cyclin-dependent kinase inhibitor fadraciclib (CYC065) depletes anti-apoptotic protein and synergizes with venetoclax in primary chronic lymphocytic leukemia cells**". Fadraciclib is Cyclacel's novel CDK2/9 inhibitor, currently in two Phase 1/2 trials, one for the treatment of advanced solid tumors and lymphomas and another for hematological malignancies, including patients with leukemia being treated in combination with venetoclax.

"Results from this research provide further mechanistic evidence in support of our ongoing Phase 1/2 clinical study of oral fadraciclib in select hematological malignancies," said Mark Kirschbaum, M.D., Senior Vice President and Chief Medical Officer of Cyclacel. "The findings confirmed that fadraciclib suppresses MCL1 and synergizes with venetoclax, the only FDA-approved apoptosis enabling leukemia treatment. We have included a cohort within the proof-of-concept part of our Phase 1/2 study that will evaluate the combination of fadraciclib plus venetoclax in patients who have previously failed venetoclax-based regimens."

Researchers from the Department of Experimental Therapeutics and the Department of Leukemia at The University of Texas MD Anderson Cancer Center published preclinical data interrogating fadraciclib's mechanism of action against primary cell lines of chronic lymphocytic leukemia (CLL), both as a single agent and in combination with the BCL2 antagonist, venetoclax.

Results from the study confirmed that fadraciclib inhibited CDK9 mediated transcription, reduced levels of the short-lived anti-apoptotic protein MCL1, and induced apoptosis in primary CLL cells. The data highlighted the importance of continuous treatment to prevent recovery of MCL1 protein levels. Fadraciclib is the only transcriptional CDK inhibitor in clinical development that is being dosed on a daily schedule by mouth.

Fadraciclib was shown to combine synergistically with venetoclax, the only FDA-approved apoptosis enabling, leukemia treatment. Furthermore, it was demonstrated that the best synergy, with fadraciclib and venetoclax given at the same time, was achieved in 17p deleted CLL cells, which were not sensitive to either agent alone.

Fadraciclib also overcame protection mediated by stroma CLL cells and lymph node microenvironment. This may be important for clinical translation as venetoclax appears to be less effective in the lymph nodes.[1]

The data support the rationale for pursuing clinical development of fadraciclib, either alone or in combination with a BCL2 antagonist, for the treatment of CLL.

Phase 1/2 Study in Hematological Malignancies (065-102; NCT#05168904)
A Phase 1/2 registration-directed trial, testing oral fadraciclib in various hematological malignancies is currently enrolling patients. The trial uses a streamlined design and will determine the recommended Phase 2 dose (RP2D) for single-agent, oral fadraciclib and then enter into proof-of-concept, cohort stage, using a Simon 2-stage design, where fadraciclib will be administered, both as a single agent and in combinations, 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 myelodysplastic syndromes (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 CLL who have progressed after at least two lines of therapy including a BTK inhibitor and/or venetoclax.

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

Phase 1/2 Study in Advanced Solid Tumors and Lymphomas (065-101; NCT#04983810)
In this ongoing study of fadraciclib 12 patients have been treated in four dose escalation levels. The proof-of-concept stage includes 7 histologically defined cohorts thought to be sensitive to the drug's mechanism: breast, colorectal (including KRAS mutant), endometrial/ uterine, hepatobiliary, ovarian cancers and lymphomas. An additional basket cohort will enroll patients regardless of histology with biomarkers relevant to the drug's mechanism, including MCL1, MYC and/or cyclin E amplified.

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. Preclinical data have 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 over 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.[2]

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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[1] Thijssen R, Anderson MA, Teh C, Trussart M, Blombery P, Birkinshaw R, et al. Resistance to venetoclax in chronic lymphocytic leukemia (CLL). Exp Hematol. 2019;76:S88.

[2] 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.