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# Cyclacel's CYC065 Demonstrates Promising Activity in Uterine Serous Carcinoma in Preclinical Data Published by Independent Academic Researchers

*- Data support CYC065 as potential treatment for chemotherapy-resistant, CCNE1-amplified, uterine serous carcinoma (USC); 90% of tumor samples overexpressed cyclin E1 (CCNE1) -*

BERKELEY HEIGHTS, N.J., Aug. 02, 2016 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (Nasdaq:CYCC) (Nasdaq:CYCCP) ("Cyclacel" or the "Company"), a biopharmaceutical company developing oral therapies that target various phases of cell cycle control for the treatment of cancer and other serious disorders today announced the publication of a paper by researchers at Yale University with promising preclinical data related to CYC065, Cyclacel's second generation cyclin-dependent kinase CDK2/9 inhibitor. The paper, titled "Dual CCNE1/PIK3CA targeting is synergistic in CCNE1-amplified/PIK3CA-mutated uterine serous carcinomas *in vitro* and *in vivo*" is published in the July 2016 issue of the British Journal of Cancer (www.nature.com/bjc/journal/v115/n3/abs/bjc2016198a.html).

In this investigator-sponsored preclinical study, the authors investigated the potential of cyclin E1 (CCNE1) amplification and PIK3CA driver mutations, both common in uterine serous carcinoma (USC), as therapeutic targets. The paper demonstrated that CYC065, alone and in combination with the investigational PIK3CA inhibitor taselisib, may have potential as a treatment option in USC.

The authors found that 89.5% of USC tumor samples overexpressed the cyclin E1 (CCNE1) gene, which transcribes the cyclin E partner of CDK2, and is responsible for cellular proliferation. As a potent and selective CDK2/9 inhibitor, CYC065 was investigated as a new treatment option for this aggressive type of endometrial cancer. The researchers reported that CYC065 not only inhibited cellular proliferation of CCNE1-amplified USC models *in vitro* but also reduced tumor growth in murine xenograft models. Importantly, the researchers found CCNE1 expression to significantly correlate with sensitivity to CYC065 *in vitro* and the cellular mechanism of action, namely accumulation of cells in G1 phase, was consistent with inhibition of the CDK2-cyclin E complex in CCNE1 amplified USC cell lines.

Furthermore, mutations to the Her2/PI3K/AKT/mTOR signaling pathway frequently coincide with CCNE1-amplifications in USC. To address this form of USC, the researchers reported, that combination treatment using CYC065 and the investigational PI3KCA inhibitor, taselisib, was synergistic, resulting in a significant reduction in tumor growth in murine xenograft models of CCNE1-amplified/PIK3CA-mutated USC.

"Treatment options for patients with these aggressive endometrial cancers are limited," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel, "we are encouraged by these preclinical data showing that CYC065 alone or in combination inhibits USC tumor growth. Upregulation of CCNE1 has been reported for many human cancers, including breast, colon, gastric, lung and high-grade ovarian, and has been correlated with poor prognosis and drug resistance. These findings provide strong rationale for the use of CYC065 to target the CDK2-cyclin E complex in such cancers and warrants further investigation in tumors with amplified/overexpressed CCNE1. The findings are consistent with previously reported preclinical data that CYC065 reverses cyclin E-mediated resistance to trastuzumab in breast cancer. We look forward to reporting data from the ongoing first-in-human, Phase 1 study of CYC065 in solid tumors and lymphomas."

**About CYC065**

CYC065 is a highly-selective, orally- and intravenously-available, second generation inhibitor of CDK2 and CDK9 and causes apoptotic death of cancer cells at sub-micromolar concentrations. Antitumor efficacy has been achieved in vivo with once a day oral dosing at well tolerated doses. Evidence from published nonclinical studies show that CYC065 may benefit patients with adult and pediatric hematological malignancies, including certain Acute Myeloid Leukemias (AML), Acute Lymphocytic Leukemias (ALL), Chronic Lymphocytic Leukemias (CLL), B-cell lymphomas, multiple myelomas, and certain solid tumors, including breast and uterine cancers. Independent investigators published nonclinical evidence that CYC065 induced regression or tumor growth inhibition in a model of HER2-positive breast cancer addicted to cyclin E that is resistant to trastuzumab (Herceptin®), and that CYC065 reduced tumor growth in models of CCNE1-amplified uterine serous carcinoma.

CYC065 is mechanistically similar but has much higher dose potency, *in vitro* and *in vivo*, improved metabolic stability and longer patent protection than seliciclib, Cyclacel's first generation CDK inhibitor. Translational biology data support development of CYC065 as a stratified medicine for solid and liquid cancers. CYC065 has been shown to reverse drug resistance associated with the addiction of cancer cells to cyclin E and may inhibit CDK9-dependent oncogenic and leukemogenic pathways, including malignancies driven by certain oncogenes and mixed lineage leukemia rearrangements (MLL-r). CYC065 causes prolonged down regulation of the Mcl-1-mediated pro-survival pathway in cancer cells.

**About Cyclacel Pharmaceuticals, Inc.**

Cyclacel Pharmaceuticals is a clinical-stage biopharmaceutical company using cell cycle control and DNA damage response biology to develop innovative, targeted medicines for cancer and other proliferative diseases. The SEAMLESS randomized Phase 3 trial of sapacitabine as front-line treatment for AML in the elderly under an SPA with FDA has completed

enrollment. Cyclacel's pipeline includes an oral combination of seliciclib (CDK2/9 inhibitor) and sapacitabine in Phase 1 in advanced solid tumors including patients with BRCA mutations; sapacitabine in Phase 2 in MDS; and CYC065 (CDK2/9 inhibitor) in Phase 1 in solid tumors and lymphomas with potential utility based on preclinical data in other hematological malignancies. Cyclacel's strategy is to build a diversified biopharmaceutical business focused in hematology and oncology based on a pipeline of novel drug candidates. Please visit www.cyclacel.com for more information.

**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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