Publication Identifies Cyclin E as Key Resistance Pathway to Breast Cancer Treated by CDK4/6 Inhibitors and Thereby Amenable to Treatment by CYC065 CDK2/9 Inhibitor

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-- PALOMA-3 study gene expression profiling shows that CDK2 is a key kinase bypass mechanism after treatment with palbociclib plus hormone therapy --

-- Cyclin E is proposed as the first predictive biomarker of palbociclib efficacy --

BERKELEY HEIGHTS, N.J., March 25, 2019 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (Nasdaq:CYCC) (Nasdaq:CYCCP) (Cyclacel or the Company), a biopharmaceutical company developing innovative medicines based on cancer cell biology, highlighted a paper from independent investigators titled *Cyclin E1 Expression and Palbociclib Efficacy in Previously Treated Hormone Receptor–Positive Metastatic Breast Cancer* published in the most recent edition of the Journal of Clinical Oncology*(Turner N et al, 2019 https://ascopubs.org/doi/full/10.1200/JCO.18.00925)*. The study findings identify overexpression of cyclin E1 as a mechanism by which breast cancer escapes the effects of palbociclib CDK4/6 inhibitor (Ibrance®) plus fulvestrant treatment. Inhibition of the CDK2/cyclin E complex, the target of Cyclacel's CYC065 clinical stage candidate, is proposed as a potential therapeutic approach to prevent early progression on CDK4/6 inhibitors.

"These data from a successful, randomized Phase 3 study identifies cyclin E as a biomarker of resistance of estrogen receptor positive, HER-2 negative breast cancer to palbociclib regimens. This supports and extends previous data showing that cyclin E is a resistance mechanism to HER-2 positive breast and uterine cancer treated with trastuzumab," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "Preclinical data demonstrated CYC065 activity in cyclin E amplified models of palbociclib-resistant breast cancer. Tumor shrinkage and stable disease were observed in four patients with cyclin E amplified advanced cancers in a first-in-human, Phase 1 study of single agent CYC065. Cyclin E amplified tumors are found in patients with gynecological and other cancers and represent a large, unmet medical need. The findings support CYC065's broad therapeutic potential and unique target profile among CDK inhibitors."

In the PALOMA-3 trial (NCT01942135), patients with endocrine therapy-pretreated, metastatic breast cancer were randomized to receive palbociclib + fulvestrant or placebo + fulvestrant. Out of 521 patients treated 302 had tumor tissue analyzed. Palbociclib efficacy was approximately halved in patients with high compared to low cyclin E1 expression in their tumors (median PFS of 7.6 vs. 14.1 months respectively). In contrast to cyclin E1 expression, the analysis showed that expression of cyclin D1, the molecular partner of CDKs 4 and 6 which are the targets of palbociclib, or PI3 kinase (PIK3CA) mutations were not predictive of efficacy for palbociclib plus hormone therapy.

The findings were further validated through a gene expression analysis of the Preoperative Palbociclib (POP) trial in 61 patients with untreated early-stage breast cancer receiving either palbociclib until the day before surgery or no treatment. High cyclin E expression was associated with lower absolute antiproliferative response to palbociclib (high 36%; intermediate 79%; low 80%; P = 0.005). Correlative analysis of PALOMA-3 data has identified cyclin E1 as the first potential biomarker that is predictive of the efficacy of palbociclib.

About CYC065

CYC065 is a highly-selective, orally- and intravenously-available, 2nd generation inhibitor of cyclin dependent kinases (CDK) 2 and 9. CYC065 is in an ongoing Phase 1, first-in-human study in patients with advanced solid tumors. In this study target engagement and durable suppression of the Mcl-1 biomarker were observed after a single dose of CYC065. Tumor shrinkage and stable disease were observed in four patients with cyclin E amplified advanced cancers. CYC065 is also being evaluated in a Phase 1 study in combination with venetoclax in patients with relapsed/refractory CLL. Preclinical data suggest that CYC065 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 HER2+ breast cancer, uterine serous carcinoma and neuroblastoma.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel Pharmaceuticals is a clinical-stage biopharmaceutical company using its expertise in cell cycle, transcriptional regulation and DNA damage response biology in cancer cells to develop innovative medicines. The transcriptional regulation program is evaluating CYC065, a CDK inhibitor, in patients with advanced solid cancers and in combination with venetoclax in patients with advanced hematological malignancies, including CLL and AML. The DNA damage response program is evaluating a sequential regimen of sapacitabine and seliciclib, a CDK inhibitor, in BRCA positive patients with advanced solid cancers and a concomitant regimen of sapacitabine and olaparib, a PARP inhibitor, in BRCA positive patients with breast cancer. CYC140, a PLK inhibitor, is in a Phase 1 first-in-human study in patients with advanced leukemias. 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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