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Cyclacel's CYC065 Demonstrates Promising Activity in MYCN-Addicted Neuroblastoma in Preclinical Data Presented at Childhood Cancer 2016

Data support CYC065 as potential treatment for MYCN amplified/overexpressed neuroblastoma

BERKELEY HEIGHTS, N.J., Sept. 06, 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 presentation of preclinical data demonstrating that both Cyclacel's CYC065, a clinical stage, second generation, cyclin-dependent kinase CDK2/9 inhibitor, and CCT68127, a preclinical stage CDK2/9 inhibitor, prolong survival in *MYCN*-addicted neuroblastoma models. The data were presented at the Childhood Cancer Meeting, September 5 — 7th in London, UK.

"This study adds to the growing evidence of the value of CDK inhibition as an approach to treating cancer. *MYCN* is an important therapeutic target in oncology and a major oncogenic driver of neuroblastoma, a childhood cancer. There are no approved drugs that act against *MYCN* or MYC proteins," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "We are encouraged by the preclinical data, which extend and support earlier findings, showing that CYC065 and CCT68127 reduce *MYCN* transcription and protein levels and have antitumor activity in neuroblastoma models. Additionally, we have demonstrated in other preclinical studies, that our transcriptional CDK2/9 inhibitors target key molecular features of cancers with poor prognosis, such as MLL-r leukemias or MYC-driven lymphomas. Furthermore, evidence from early clinical trials show that CDK2/9 inhibitors can have a synergistic effect with other anticancer agents. We look forward to reporting data from our ongoing Phase 1 study of CYC065 in patients with solid tumors."

In this preclinical study, an international group of researchers led by Prof. Louis Chesler from The Institute of Cancer Research, London, explored *in vitro* and *in vivo* the sensitivity of neuroblastoma cells to CYC065 and CCT68127. Neuroblastoma cells with *MYCN* amplification and overexpression were found to be particularly sensitive to both CDK2/9 inhibitors. The mechanism of action of CYC065 and CCT68127 included inhibition of *MYCN* transcription, downregulation of N-MYC protein, blocking neuroblastoma cell proliferation and induction of apoptosis. Treatment with either CYC065 or CCT68127 significantly reduced tumor burden and prolonged survival in several neuroblastoma models *in vivo*.

Citation

Poon E, Jamin Y, Walz S, Hakkert S, Kwok C, Hallsworth A, Thway K, Barker K, Sbirkov Y, Pickard L, Urban Z, Tardif N, Webber H, Box G, Valenti M, De Haven Brandon A, Petrie K, Ebus M, Molenaar J, Eccles S, Robinson SP, Zheleva D, Eilers M, Workman P, Chesler L. The small molecule CDK2 and CDK9 inhibitors CYC065 and CCT68127 are potent inhibitors of MYCN via transcriptional repression. Childhood Cancer Meeting 2016, September 5 — 7th, London, UK, Abs. 1-19.

About *MYCN*

The *MYCN* gene encodes a transcription factor that is expressed in fetal brain and neural crest and is critical for normal development of the brain and nerves. The *MYCN* oncogene is over-expressed in a number of different types of cancer, most notably neuroblastoma, and also rhabdomyosarcoma, medulloblastoma, astrocytoma, Wilms' tumor and small cell lung cancer. Amplification of the *MYCN* oncogene is the most common genomic alteration in aggressive neuroblastomas and is associated with poor clinical outcome. There are no approved drugs that directly target *MYCN* prompting the investigation of indirect approaches such as exploitation of a synthetic lethal relationship between *MYCN* amplification/overexpression and inhibition of CDK2.

About Neuroblastoma

According to the American Cancer Society, neuroblastoma is the most common cancer in infants less than one year old and it accounts for about six percent of all pediatric cancers or about 700 cases per year. The disease has a fatal outcome in one out of every seven children diagnosed with it. Preclinical data from an international investigator group demonstrated that Cyclacel's CYC065 and CCT68127 target *MYCN* gene expression and have potent *in vitro* and *in vivo* anti-tumor activities, suggesting therapeutic potential in neuroblastoma, including high-risk patients with *MYCN* amplification.

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, reduced tumor growth in models of CCNE1-amplified uterine serous carcinoma and reduced tumor burden and prolonged survival in several neuroblastoma models *in vivo*.

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 sapacitabine and seliciclib (CDK2/9 inhibitor) 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 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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