April 18, 2016

Cyclacel's Second-Generation CDK2/9 Inhibitor, CYC065, is an Effective Inducer of Cell Death in B-cell Lymphoma and Synergizes With Bcl-2 or BET Inhibitors

Preclinical Data Presented at the AACR 2016 Meeting

BERKELEY HEIGHTS, N.J., April 18, 2016 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (NASDAQ:CYCC) (NASDAQ:CYCCP) (Cyclacel or the Company), today announced the presentation of preclinical data demonstrating therapeutic potential of CYC065, the Company's second-generation, cyclin-dependent kinase (CDK) 2/9 inhibitor, as a targeted anti-cancer agent. The data show that CYC065 can induce cell death and combined beneficially with anti-cancer drugs from the Bcl-2 and BET inhibitor classes, in *in vitro* models of B-cell lymphoma, including double-hit lymphomas. The data were presented at the American Association for Cancer Research (AACR) Annual Meeting 2016, April 16 - 20, 2016, in New Orleans.

"CYC065 is currently in a Phase 1 clinical trial to evaluate its safety, pharmacokinetic and pharmacodynamic activity in patients with solid tumors and lymphomas," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "Data presented at AACR highlights its potential as an agent to treat hematological malignancies, such as B-cell lymphoma. Data from this study are particularly important as they validate the mechanism of action of CYC065, which is reducing MYC and Mcl-1 levels, both of which can be elevated in B-cell lymphoma. The study also suggests that CYC065 may be used effectively in combination with other targeted anti-tumor agents in lymphomas. In parallel with collecting preclinical data, we continue to enroll patients in the Phase 1 trial and look forward to reporting initial results from the clinical study."

Double-hit B-cell lymphomas, defined by concurrent *MYC* and *BCL2* rearrangements, have poor prognosis compared to standard-risk diffuse large B-cell lymphomas (DLBCL). There is a need for novel treatments specifically exploiting molecular features of the disease. DLBCL show frequent overexpression of Mcl-1, 50% in ABC and 30% in GCB subtypes respectively. MYC-driven lymphomas are highly sensitive to depletion of Mcl-1. MYC overexpression and CDK inhibition have shown synthetic lethality.

The preclinical study evaluated both single-agent activity of CYC065 and combinations of CYC065 with the Bcl-2 inhibitor, venetoclax (ABT-199, Venclexta®), and BET (Bromodomain and Extra-Terminal) inhibitors in B-cell lymphoma cell lines. Short exposure to CYC065 was sufficient to downregulate MYC, an oncogene aberrantly expressed in many cancers, and Mcl-1, an anti-apoptotic member of the Bcl-2 family, and to induce cell death. CYC065 treatment had no impact on Bcl-2 levels. Combinations of CYC065 with venetoclax or BET inhibitors were both synergistic. CYC065 targets key oncogenic and survival pathways in double-hit B-cell lymphomas suggesting a therapeutic rationale for this indication.

Abstract:	1309
Title:	CYC065, a novel CDK2/9 inhibitor, is an effective inducer of cell death and synergizes with BCL2 and BET inhibitors in B-cell lymphoma, including double-hit lymphomas
Date/Time:	Monday, April 18, 2016 8 a.m. - 12 p.m. CDT
Location:	Section 18, Poster Board 28
Session Title:	Regulation of Anticancer Drug Effects
Authors:	Sheelagh M. Frame, Elizabeth Pohler, Craig MacKay, Daniella Zheleva, David Blake, Cyclacel Limited, Dundee, UK

The abstract can be accessed through the AACR website, www.aacr.org.

About CDK Inhibition

CDK enzymes, in particular CDK2, 4, 6 and 9, play pivotal roles in cancer cell growth, survival, metastatic spread and repair of DNA damage. Pharmacological inhibition of CDK2/9 has been shown to have potent anticancer effects in certain cancer types, including some that are resistant to approved treatments. CDK2/9 inhibitors have been shown to induce apoptosis, or programmed death of cancer cells, whereas CDK4/6 inhibitors, such as palbociclib (Ibrance®), induce senescence or dormancy of cancer cells. Senescence may be associated with emergence of resistance.

About CYC065 (second generation CDK inhibitor)

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 as a single-agent can induce tumor growth delay to HER2-positive breast cancer cells addicted to cyclin E, the partner protein of CDK2, and resistant to trastuzumab (Herceptin®), while administration of CYC065 in combination with trastuzumab resulted in regression or sustained tumor growth inhibition.

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.

A grant of approximately $1.9 million from the U.K. government's Biomedical Catalyst has supported IND-directed development of CYC065.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel is a biopharmaceutical company developing oral therapies that target the various phases of cell cycle control for the treatment of cancer and other serious diseases. Sapacitabine, Cyclacel's most advanced product candidate, is the subject of SEAMLESS, a Phase 3 trial, which has completed enrollment and is being conducted under an SPA with the U.S. Food and Drug Administration (FDA) as front-line treatment for acute myeloid leukemia (AML) in the elderly, and other indications, including myelodysplastic syndromes (MDS). Cyclacel's pipeline includes an oral regimen of seliciclib in combination with sapacitabine in a Phase 1 study of patients with solid tumors, including BRCA positive cancers, and CYC065, a novel CDK2/9 inhibitor, in a Phase 1 study of patients with solid tumors and lymphomas with potential utility in both hematological malignancies and solid tumors. Cyclacel's strategy is to build a diversified biopharmaceutical business focused in hematology and oncology based on a development 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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