April 20, 2015

Cyclacel's Second-Generation CDK2/9 Inhibitor, CYC065, Demonstrates Therapeutic Potential and Synergy With Other Anti-Cancer Compounds

In Vitro and in Vivo Preclinical Data Presented at the AACR 2015 Meeting Show Selectivity and Anti-Cancer Activity of CYC065

BERKELEY HEIGHTS, N.J., April 20, 2015 (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 showed that CYC065 inhibits key cancer and leukemia survival mechanisms and causes death by apoptosis in cancer cells. CYC065 is effective against acute myeloid leukemia (AML), and in particular, AML with genetic abnormalities such as MLL rearrangements (MLL-r), which confer a poor prognosis. CYC065 was also effective against uterine cancer cells including those resistant to chemotherapy and was especially potent in uterine cancer cells in which cyclin E, the partner protein of CDK2, was amplified or overexpressed. In each case CYC065 showed synergy with available anti-cancer agents. The data were presented at the American Association for Cancer Research (AACR) Annual Meeting 2015, April 18 - 22, 2015, in Philadelphia. Results from preclinical studies by independent investigators on the Company's drug candidates sapacitabine and seliciclib, as well as CYC065, are also being presented.

"The AACR presentations on our CDK inhibitors underscore our efforts over many years in cyclin- and CDK-based cell cycle biology," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "CYC065 is on an IND-track and the data presented demonstrate its potency and selectivity highlighting potential clinical development pathways. We believe that CYC065's CDK profile is an important differentiator. Cyclacel's founder, Prof. Sir David Lane, Ph.D., strongly advocated targeting CDK2/9 as a promising anti-cancer strategy. CDK2/9 inhibitors induce 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. We are grateful to the UK Government's Biomedical Catalyst for the $1.9 million grant support to bring CYC065 to the IND stage. In addition to allocating resources for the Phase 1 study of CYC065, we have adequate resources to follow-up patients in our Phase 3 SEAMLESS study of sapacitabine until mature data can be analyzed. We estimate this to occur between the second half of 2015 and the first half of 2016."

Preclinical data show that CYC065 may reverse drug resistance associated with addiction of cancer cells to cyclin E. CYC065 may also inhibit CDK9-dependent oncogenic and leukemogenic pathways, including malignancies driven by certain oncogenes and MLL-r. In their AACR presentation, Cyclacel scientists provided insights on the mechanism of action, determinants of sensitivity and synergistic combinations of CYC065 in AML. The pro-apoptotic mechanism of CYC065 included rapid inhibition of transcription. MLL gene status and levels of Bcl-2 family proteins correlated with sensitivity of AML cell lines to CYC065. Short pulse treatment was sufficient to inhibit sensitive AML cells. CYC065's potent anti-cancer activity was confirmed in AML xenograft models in which tumor growth inhibition ranging from 90 to 97 percent was achieved at well-tolerated dose levels. Combination studies revealed the potential to combine CYC065 with available and experimental leukemia therapies, including cytarabine. The potent *in vitro* and *in vivo* anti-cancer activity, opportunity for patient stratification and the ability to combine with anti-leukemic agents suggest that CYC065 may have therapeutic potential in AML.

The schedule and meeting location for the sessions, together with the abstract information, are listed below by program:

CYC065

Abstract:	1650
Title:	CYC065, a novel CDK2/5/9 inhibitor: detailed mechanistic studies, determinants of sensitivity and synergistic combinations
Date/Time:	Monday, April 20, 2015 8:00 AM - 12:00 PM
Location:	Section 28, Poster Board 13
Session Title:	Cell Cycle, DNA, and Transcription Targets
Authors:	Chiara Saladino, Sheelagh Frame, Susan Davis, David Blake, Daniella Zheleva, Cyclacel Limited, Dundee, UK

Abstract:	3103

Title: Cyclin E amplification predicts sensitivity of primary Uterine Serous Carcinoma (USC) cell lines to the cdk2 inhibitor CYC065

Date/Time: Tuesday, April 21, 2015, 8:00 AM -12:00 PM

Location: Section 9, Poster Board 16

Session Title: Targeting Cyclin-Dependent Kinases and Checkpoint Kinases for Cancer Therapy

Authors: Emiliano Cocco, Stefania Bellone, Salvatore Lopez, Elena Bonazzoli, Federica Predolini, Jonathan D. Black, Alessandro D. Santin, Yale University, New Haven, CT

Seliciclib

Abstract: 2427

Title: The difference of drug sensitivity between HPV-positive and HPV-negative head and neck squamous cell carcinoma cell lines

Date/Time: Monday, April 20, 2015, 1:00 PM -5:00 PM

Location: Section 22, Poster Board 12

Session Title: Preclinical Targeted Therapy

Authors: Ming Zhang, Tuhina Mazumdar, Shaohua Peng, Pan Tong, Vaishnavi Sambandam, Lauren A. Byers, Jeffrey N. Myers, Jing Wang, Faye M. Johnson. University of Texas, MD Anderson Cancer Center, Houston, TX

Other Cyclacel CDK Inhibitors

Abstract: 942

Title: Novel CDK2/9 inhibitor has antineoplastic activity in lung cancer by inducing anaphase catastrophe

Date/Time: Sunday, April 19, 2015, 3:15 PM

Location: Room 120, Pennsylvania Convention Center

Session Title: Cell Cycle Mechanisms of Anti-cancer Drug Action

Authors: Masanori Kawakami[1], Lisa Maria Mustachio[1], Xi Liu[1], Shanhu Hu[2], Yun Lu[2], David Sekula[1], Sarah Freemantle[2], Ethan Dmitrovsky[1]. [1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Geisel School of Medicine at Dartmouth, Hanover, NH

Sapacitabine

Abstract: 2549

Title: Tyrosyl-DNA phosphodiesterase 1 (TDP1) is critical for the repair of DNA breaks induced by sapacitabine, a nucleoside antimetabolite in clinical trials targeted to ATM- and BRCA-deficient tumors

Date/Time: Monday, April 20, 2015, 1:00 PM -5:00 PM

Location: Section 28, Poster Board 1

Session Title: Damaging and Antimitotic Agents and Cytotoxicity Modulators

Authors: Muthana Al Abo[1], Xiaojun Liu[2], William Plunkett[2], Yves Pommier[1]. [1]Developmental Therapeutics Branch and Laboratory of Molecular Pharmacology, Center for Cancer Research, NCI, NIH, Bethesda, MD; [2]Department of Experimental Therapeutics, University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract: 2550

Title: FANCA protein is involved in the homologous recombination repair of sapacitabine-induced DNA damage

Date/Time: Monday, April 20, 2015, 1:00 PM -5:00 PM

Location: Section 28, Poster Board 2

Session Title: Damaging and Antimitotic Agents and Cytotoxicity Modulators

Authors: Yingjun Jiang, Xiaojun Liu, William Plunkett. UT MD Anderson Cancer Center, Houston, TX

Abstract: 2551

Title:	Brca1-deficient ovarian cancer cells are sensitized to the DNA-strand-breaking nucleoside analog sapacitabine that synergizes with PARP inhibition
Date/Time:	Monday, April 20, 2015, 1:00 PM -5:00 PM
Location:	Section 28, Poster Board 3
Session Title:	Damaging and Antimitotic Agents and Cytotoxicity Modulators
Authors:	Xiaojun Liu, Yingjun Jiang, Billie Nowak, Dariya Tikhomirova, William Plunkett. UT MD Anderson Cancer Center, Houston, TX

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

About CDK Inhibition

CDK enzymes, in particular CDKs 2, 4, 6 and 9, play pivotal roles in cancer cell growth, metastatic spread and repair of DNA damage. Pharmacological inhibition of CDK2/9 has been shown to have potent anti-cancer 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 seliciclib

Seliciclib, an orally-available CDK2/9 inhibitor, has been evaluated to date in approximately 400 patients. Seliciclib demonstrated clinical evidence of anti-cancer activity in patients with non-small cell lung cancer and nasopharyngeal cancer. It is also being explored in an ongoing Phase 1 study in combination with Cyclacel's orally-available sapacitabine in patients with solid tumors with previously reported evidence of durable tumor shrinkage in patients with breast, ovarian and pancreatic cancers.

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 of Cyclacel's CDK inhibitors 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), 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 tumors. 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 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 Homologous Recombination (HR) repair-deficient breast, ovarian and pancreatic cancers, including gBRCA positive tumors, and CYC065, a novel CDK 2/9 inhibitor, 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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