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Cyclacel Doses First Patient in Phase 1 Trial of Its Novel CDK2/9 Inhibitor, CYC065, for the Treatment of Advanced Solid Tumors

BERKELEY HEIGHTS, N.J., Oct. 22, 2015 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (NASDAQ:CYCC) (NASDAQ:CYCCP) (Cyclacel or the Company), a biopharmaceutical company developing oral therapies that target the various phases of cell cycle control for the treatment of cancer and other serious disorders today announced the dosing of the first patient in a Phase 1 trial of CYC065, the Company's novel second generation CDK (cyclin-dependent kinase) 2/9 inhibitor, for the treatment of advanced solid tumors. CYC065 was selected from the Company's discovery program in Dundee, Scotland and its development was supported in part by a UK government grant. In preclinical studies CYC065 has demonstrated anti-tumor activity as a single agent in hematological malignancies and solid tumors, including drug-resistant models. CYC065 also combined effectively with other targeted anticancer agents in drug-resistant solid tumor *in vivo* models. The objective of the Phase 1 trial is to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of CYC065 in advanced cancer patients. The trial is being conducted at the Dana Farber Cancer Institute in Boston.

"The recent accelerated approval of palbociclib, a CDK4/6 targeted inhibitor, for breast cancer demonstrates that CDK inhibitors can be an effective class of anti-cancer therapeutics," said Geoffrey I. Shapiro, M.D., Ph.D., Associate Professor of Medicine at Harvard Medical School and Director of the Early Drug Development Center, Dana Farber Cancer Institute. "CYC065 works differently from palbociclib, since it targets CDKs 2 and 9. In preclinical models, the drug induces apoptosis, or programmed death, of cancer cells irrespective of retinoblastoma (RB) pathway status and has been shown to reverse drug resistance associated with the addiction of cancer cells to cyclin E, a partner protein of CDK2. CYC065 has also been shown to inhibit CDK9-dependent oncogenic and leukemogenic pathways, such as those driven by *MYC* amplification or Mixed Lineage Leukemia gene rearrangement. Cancer cells manage to survive and evade other treatments by activating these pathways."

Spiro Rombotis, President and Chief Executive Officer of Cyclacel added, "CDK inhibitors have emerged as an important class of anti-tumor agents. Because these agents can act synergistically with other anti-cancer therapies, they may have utility when used in combination. This is the case with palbociclib, which is approved in combination with letrozole for the treatment of advanced breast cancer. Our first generation CDK2/9 inhibitor, seliciclib, has been administered to approximately 400 patients in several trials. Seliciclib demonstrated clinical evidence of anticancer activity in patients with non-small cell lung cancer and nasopharyngeal cancer. It has also shown durable activity in patients with *BRCA* mutations, when administered in combination with sapacitabine, another Cyclacel molecule. CYC065, our second generation CDK2/9 inhibitor, is mechanistically similar but has much higher potency and longer patent protection than seliciclib. Data from this study will inform the design of another Phase 1 study of CYC065 in patients with hematological tumors and are also anticipated to provide the basis for proof of concept trials in solid tumors with CYC065 in combination with other anti-cancer agents."

For further information please refer to ClinicalTrials.gov with trial identifier NCT02552953.

About CYC065 & CDK Inhibition

CYC065 is a highly-selective, second generation inhibitor of CDK2 and CDK9 that causes apoptotic death of cancer cells at sub-micromolar concentrations and is bioavailable via oral and intravenous routes. Antitumor efficacy has been achieved *in vivo* with once a day oral dosing at well tolerated doses. Evidence from published preclinical 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), Diffuse Large B-cell Lymphoma (DLBCL), Multiple Myelomas (MM), and certain solid tumors, including breast and uterine cancers.

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 CDK2/9 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, a partner protein of CDK2, and inhibit CDK9-dependent oncogenic and leukemogenic pathways, e.g. MYC and MLL-r. CYC065 also causes down regulation of the MCL-1-mediated pro-survival pathway, leading to rapid induction of apoptosis in MCL-1 dependent cancer cells.

In 2011, independent investigators published preclinical evidence that CYC065 as a single-agent can induce tumor growth delay to HER2-positive breast cancer cells addicted to cyclin E and resistant to trastuzumab (Herceptin®), while administration of CYC065 in combination with trastuzumab resulted in regression or sustained tumor growth inhibition.

MLL gene status and levels of Bcl-2 family proteins correlated with sensitivity of AML cell lines to CYC065. Combination studies revealed the potential to combine CYC065 with available and experimental leukemia therapies, including cytarabine and Bcl-2 inhibitors. Potent anticancer activity of CYC065 was demonstrated *in vivo* in AML xenograft models resulting in over 90% inhibition of tumor growth. 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.

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

CDK enzymes, in particular CDKs 2, 4, 6 and 9, play pivotal roles in cancer cell growth, 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 conventional 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 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 BRCA positive tumors, and CYC065, a novel CDK2/9 inhibitor in a Phase 1 study of patients with solid tumors and 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.

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