Cyclacel's Fadraciclib Demonstrates Efficacy in Patient-Derived Colorectal Cancer Models at the 2024 ASCO Annual Meeting

June 4, 2024

- Novel CDK2/9 inhibitor fadraciclib induces anaphase catastrophe, a novel cancer-specific mechanism of action -

BERKELEY HEIGHTS, N.J., June 04, 2024 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (NASDAQ: CYCC, NASDAQ: CYCCP; "Cyclacel" or the "Company"), a biopharmaceutical company developing innovative medicines based on cancer cell biology, today announced a presentation by independent investigators of preclinical data demonstrating therapeutic potential of fadraciclib, the Company's cyclin-dependent kinase (CDK) 2/9 inhibitor, as a novel treatment for metastatic colorectal cancer (CRC). The data show that fadraciclib substantially inhibited growth, triggered apoptosis, and induced anaphase catastrophe in CRC patient-derived organoids (PDOs) and xenografts (PDX). The data were presented at a poster at the American Society of Clinical Oncology (ASCO) Annual Meeting from May 31-June 4, 2024 in Chicago, IL.

"This presentation further supports fadraciclib's broad potential in multiple tumor types by targeting key molecular features of cancer," said Spiro Rombotis, President and Chief Executive officer. "As previously announced, we have begun the proof of concept part of the 065-101 study in which we are selecting patients with alterations in certain tumor suppressor genes and also patients with T-cell lymphoma. We look forward to reporting initial proof of concept data in the second half of 2024."

In the preclinical study, a group of researchers led by David S. Hsu, MD, PhD, Associate Professor of Medicine, Department of Medicine, Division of Medical Oncology, Duke University, explored the potential efficacy of fadraciclib as a novel treatment for CRC.

Eighteen CRC PDOs generated from patients undergoing biopsy or resection for their primary or metastatic CRC were treated with standard of care chemotherapy (oxaliplatin, irinotecan (SN38) and 5-Fluorouracil), palbociclib (CDK4/6 inhibitor), or fadraciclib, to determine sensitivity to each drug. Subsequently, three matching, patient-derived xenografts (PDXs) were generated for *in vivo* validation and treated with fadraciclib via oral gavage at a dose of 25 mg/kg twice daily, five days a week for two weeks. Target validation for CDK2/9 inhibition and induction of apoptosis was performed via western blotting, cell cycle arrest was determined via flow cytometry, and induction of anaphase catastrophe was determined by immunofluorescence staining.

The data showed that CRC PDOs were more sensitive to fadraciclib treatment than either chemotherapy or palbociclib. The investigators demonstrated fadraciclib's ability to inhibit both CDK2 and CDK9, cause anaphase catastrophe, downregulate MYC protein levels and induce apoptosis. These findings translated to significant tumor growth inhibition by fadraciclib in matched CRC PDX models. The study concluded that fadraciclib has potential as a therapy for advanced CRC and that CDK2/9 inhibition impacts multiple critical pathways involved in transcription, mitosis and apoptosis.

Anaphase catastrophe is a novel mechanism of action which offers an innovative approach to combat aneuploid cancer cells containing abnormal numbers of chromosomes. The data provides further support to fadraciclib's potential to target key molecular features of cancer.

Details of the presentations are as follows:

Title:	Efficacy of fadraciclib (CYC065), a novel dual CDK2/9 inhibitor, on patient derived models of colorectal cancer
Abstract No. for Publication:	3596
Session Title:	Poster Session – Gastrointestinal Cancer – Colorectal and Anal
Date and Time:	June 1, 2024, 1:30 PM - 4:30 PM CDT

About Colorectal Cancers

Colorectal cancer (CRC) is the third most common type of cancer among adults in the United States. Because of the heterogeneous nature of the disease and the limited number of available treatments, there is an unmet need to identify new therapeutic vulnerabilities for advanced CRC.

About Cyclin-Dependent Kinases and Fadraciclib

Cyclin-dependent kinases (CDKs) are critical for cell cycle control and transcriptional regulation. Dysregulated CDKs have been linked to the cancer hallmarks of uncontrolled proliferation and increased cancer cell survival. Fadraciclib is a highly selective, potent, orally and intravenously available, next generation inhibitor of CDK2 and CDK9. By inhibiting CDK2 and CDK9 fadraciclib causes apoptotic death through anaphase catastrophe of cancer cells at sub-micromolar concentrations.

To date single agent activity, including CR, PR and SD, has been observed in patients with advanced endometrial, squamous non-small cell lung, ovarian and pancreatic cancers and also T-cell lymphoma. In an earlier Phase 1 study of intravenous (IV) fadraciclib, a heavily pretreated endometrial cancer patient with CDKN2A, CDKN2B and MTAP loss achieved confirmed CR and remained on treatment for approximately three years.

065-101 Study of Oral Fadraciclib

Oral fadraciclib is being tested in a Phase 1/2 trial for the treatment of advanced solid tumors and lymphoma (065-101; NCT#04983810). A total of 47 patients have been treated as monotherapy in the dose escalation part of this ongoing study which enrolled unselected, all comer patients with advanced solid tumors and lymphoma.

Cyclacel is currently enrolling the proof of concept part of the 065-101 study which is designed to further evaluate fadra safety and efficacy in up to 8 cohorts defined by histology and/or genomic profile. Initial cohorts include a biomarker cohort for patients prospectively selected for CDKN2A/CDKN2B alterations and patients with advanced T-cell lymphoma. The study is powered to demonstrate response in the molecular subtype suggested by Phase 1 data and others that may be sensitive.

CDKN2A, CDKN2B alterations

The majority of CDKN2A/B alterations are deletions or loss of function mutations. CDKN2A gene deletions occur in over 10% of several solid tumors, including glioma, head and neck, pancreatic, esophageal, lung (incl. squamous), bladder, hepatobiliary, breast, melanoma, sarcoma, and others. CDKN2A deletions have been reported in 46% of patients with PTCL-NOS, a subtype of lymphoma. CDKN2B deletions occur in over 10% of several solid tumors, including bladder, glioma, lung (incl. squamous), head and neck, pancreatic, melanoma, esophageal, sarcoma, hepatobiliary, breast, ovarian and others.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel is a clinical-stage, biopharmaceutical company developing innovative cancer medicines based on cell cycle, transcriptional regulation and mitosis biology. The transcriptional regulation program is evaluating fadraciclib, a CDK2/9 inhibitor, and the anti-mitotic program CYC140, a PLK1 inhibitor, in patients with both solid tumors and hematological malignancies. Cyclacel's strategy is to build a diversified biopharmaceutical business based on a pipeline of novel drug candidates addressing oncology and hematology indications. 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, statements related to the intended use of proceeds from the private placement, 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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